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Preface

Human Anatomy and Physiology is designed for the two-semester anatomy and physiology course taken by life science and allied health students. The textbook follows the scope and sequence of most Human Anatomy and Physiology courses, and its coverage and organization were informed by hundreds of instructors who teach the course. Instructors can customize the book, adapting it to the approach that works best in their classroom. The artwork for this textbook is aimed focusing student learning through a powerful blend of traditional depictions and instructional innovations. Color is used sparingly, to emphasize the most important aspects of any given illustration. Significant use of micrographs from the University of Michigan complement the illustrations, and provide the students with a meaningful alternate depiction of each concept. Finally, enrichment elements provide relevance and deeper context for students, particularly in the areas of health, disease, and information relevant to their intended careers.

Welcome to *Anatomy and Physiology*, an OpenStax resource. This textbook was written to increase student access to high-quality learning materials, maintaining highest standards of academic rigor at little to no cost.

About OpenStax

OpenStax is a nonprofit based at Rice University, and it's our mission to improve student access to education. Our first openly licensed college textbook was published in 2012, and our library has since scaled to over 25 books for college and AP[®] courses used by hundreds of thousands of students. Our adaptive learning technology, designed to improve learning outcomes through personalized educational paths, is being piloted in college courses throughout the country. Through our partnerships with philanthropic foundations and our alliance with other educational resource organizations, OpenStax is breaking down the most common barriers to learning and empowering students and instructors to succeed.

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Format

You can access this textbook for free in web view or PDF through openstax.org, and in low-cost print and iBooks editions.

About Anatomy and Physiology

Coverage and Scope

The units of our *Anatomy and Physiology* textbook adhere to the scope and sequence followed by most two-semester courses nationwide. The development choices for this textbook were made with the guidance of hundreds of faculty who are deeply involved in teaching this course. These choices led to innovations in art, terminology, career orientation, practical applications, and multimedia-based learning, all with a goal of increasing relevance to students. We strove to make the discipline meaningful and memorable to students, so that they can draw from it a working knowledge that will enrich their future studies.

Unit 1: Levels of Organization

Chapters 1–4 provide students with a basic understanding of human anatomy and physiology, including its language, the levels of organization, and the basics of chemistry and cell biology. These chapters provide a foundation for the further study of the body. They also focus particularly on how the body's regions, important chemicals, and cells maintain homeostasis.

Chapter 1 An Introduction to the Human Body

Chapter 2 The Chemical Level of Organization

Chapter 3 The Cellular Level of Organization

Chapter 4 The Tissue Level of Organization

Unit 2: Support and Movement

In Chapters 5–11, students explore the skin, the largest organ of the body, and examine the body's skeletal and muscular systems, following a traditional sequence of topics. This unit is the first to walk students through specific systems of the body, and as it does so, it maintains a focus on homeostasis as well as those diseases and conditions that can disrupt it.

Chapter 5 The Integumentary System

Chapter 6 Bone and Skeletal Tissue

Chapter 7 The Axial Skeleton

Chapter 8 The Appendicular Skeleton

Chapter 9 Joints

Chapter 10 Muscle Tissue

Chapter 11 The Muscular System

Unit 3: Regulation, Integration, and Control

Chapters 12–17 help students answer questions about nervous and endocrine system control and regulation. In a break with the traditional sequence of topics, the special senses are integrated into the chapter on the somatic nervous system. The chapter on the neurological examination offers students a unique approach to understanding nervous system function using five simple but powerful diagnostic tests.

Chapter 12 Introduction to the Nervous System

Chapter 13 The Anatomy of the Nervous System

Chapter 14 The Somatic Nervous System

Chapter 15 The Autonomic Nervous System

Chapter 16 The Neurological Exam

Chapter 17 The Endocrine System

Unit 4: Fluids and Transport

In Chapters 18–21, students examine the principal means of transport for materials needed to support the human body, regulate its internal environment, and provide protection.

Chapter 18 Blood

Chapter 19 The Cardiovascular System: The Heart

Chapter 20 The Cardiovascular System: Blood Vessels and Circulation

Chapter 21 The Lymphatic System and Immunity

Unit 5: Energy, Maintenance, and Environmental Exchange

In Chapters 22–26, students discover the interaction between body systems and the outside environment for the exchange of materials, the capture of energy, the release of waste, and the overall maintenance of the internal systems that regulate the exchange. The explanations and illustrations are particularly focused on how structure relates to function.

Chapter 22 The Respiratory System

Chapter 23 The Digestive System

Chapter 24 Nutrition and Metabolism

Chapter 25 The Urinary System

Chapter 26 Fluid, Electrolyte, and Acid–Base Balance

Unit 6: Human Development and the Continuity of Life

The closing chapters examine the male and female reproductive systems, describe the process of human development and the different stages of pregnancy, and end with a review of the mechanisms of inheritance.

Chapter 27 The Reproductive System

Chapter 28 Development and Genetic Inheritance

Pedagogical Foundation and Features

Anatomy and Physiology is designed to promote scientific literacy. Throughout the text, you will find features that engage the students by taking selected topics a step further.

Homeostatic Imbalances discusses the effects and results of imbalances in the body.

Disorders showcases a disorder that is relevant to the body system at hand. This feature may focus on a specific disorder or a set of related disorders.

Diseases showcases a disease that is relevant to the body system at hand.

Aging explores the effect aging has on a body's system and specific disorders that manifest over time.

Career Connections presents information on the various careers often pursued by allied health students, such as medical technician, medical examiner, and neurophysiologist. Students are introduced to the educational requirements for and day-to-day responsibilities in these careers.

Everyday Connections tie anatomical and physiological concepts to emerging issues and discuss these in terms of everyday life. Topics include “Anabolic Steroids” and “The Effect of Second-Hand Tobacco Smoke.”

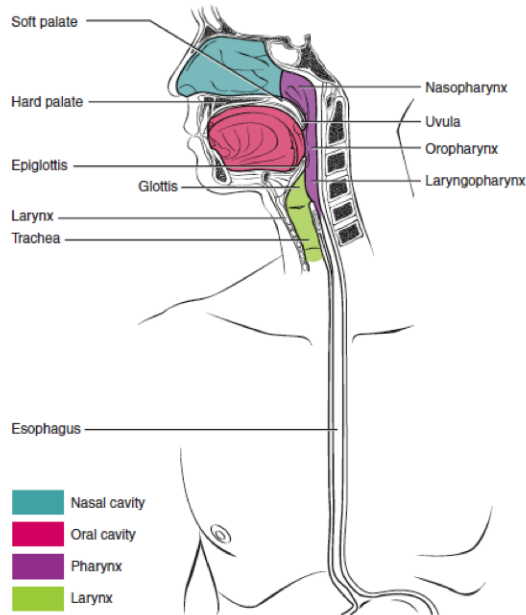
Interactive Links direct students to online exercises, simulations, animations, and videos to add a fuller context to core content and help improve understanding of the material. Many features include links to the University of Michigan’s interactive WebScopes, which allow students to zoom in on micrographs in the collection. These resources were vetted by reviewers and other subject matter experts to ensure that they are effective and accurate. We strongly urge students to explore these links, whether viewing a video or inputting data into a simulation, to gain the fullest experience and to learn how to search for information independently.

Dynamic, Learner-Centered Art

Our unique approach to visuals is designed to emphasize only the components most important in any given illustration. The art style is particularly aimed at focusing student learning through a powerful blend of traditional depictions and instructional innovations.

Much of the art in this book consists of black line illustrations. The strongest line is used to highlight the most important structures, and shading is used to show dimension and shape. Color is used sparingly to highlight and clarify the primary anatomical or functional point of the illustration. This technique is intended to draw students’ attention to the critical learning point in the illustration, without distraction from excessive gradients, shadows, and highlights. Full color is used when the structure or process requires it (for example, muscle diagrams and cardiovascular system illustrations).

The Pharynx



By highlighting the most important portions of the illustration, the artwork helps students focus on the most important points without overwhelming them.

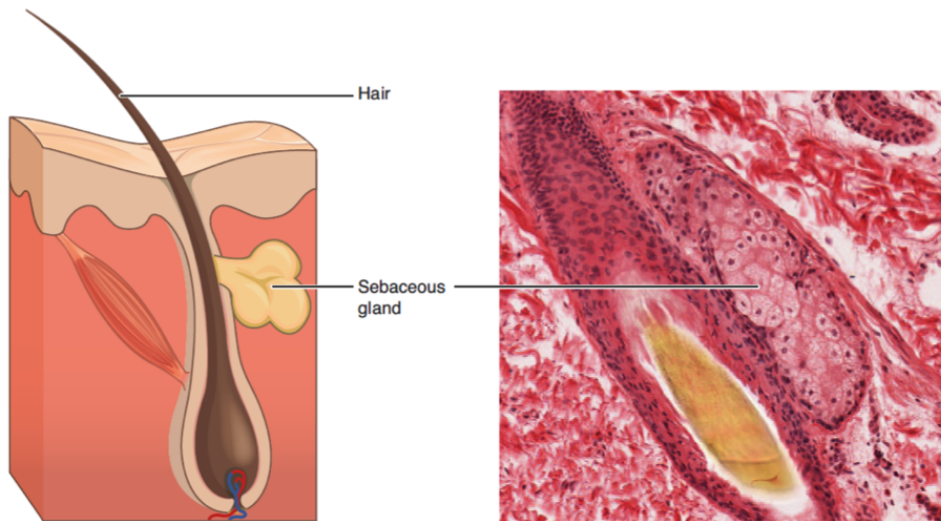
Micrographs

Micrograph magnifications have been calculated based on the objective provided with the image. If a micrograph was recorded at 40 \times , and the image was magnified an additional 2 \times , we calculated the final magnification of the micrograph to be 80 \times .

Please note that, when viewing the textbook electronically, the micrograph magnification provided in the text does not take into account the size and

magnification of the screen on your electronic device. There may be some variation.

Sebaceous Glands



These glands secrete oils that lubricate and protect the skin. LM $\times 400$. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Additional Resources

Student and Instructor Resources

We've compiled additional resources for both students and instructors, including Getting Started Guides, an instructor solution guide, and PowerPoint slides. Instructor resources require a verified instructor account, which you can apply for when you log in or create your account on openstax.org. Take advantage of these resources to supplement your OpenStax book.

Partner Resources

OpenStax Partners are our allies in the mission to make high-quality learning materials affordable and accessible to students and instructors everywhere. Their tools integrate seamlessly with our OpenStax titles at a low cost. To access the partner resources for your text, visit your book page on openstax.org.

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OpenStax wishes to thank the Regents of University of Michigan Medical School for the use of their extensive micrograph collection. Many of the UM micrographs that appear in *Anatomy and Physiology* are interactive WebScopes, which students can explore by zooming in and out.

We also wish to thank the Open Learning Initiative at Carnegie Mellon University, with whom we shared and exchanged resources during the

development of *Anatomy and Physiology*.

Introduction

class="introduction"

Blood Pressure

A
proficiency
in anatomy
and
physiology is
fundamental
to any career
in the health
professions.
(credit:
Bryan
Mason/flickr
)



Note:**Chapter Objectives**

After studying this chapter, you will be able to:

- Distinguish between anatomy and physiology, and identify several branches of each
- Describe the structure of the body, from simplest to most complex, in terms of the six levels of organization
- Identify the functional characteristics of human life
- Identify the four requirements for human survival
- Define homeostasis and explain its importance to normal human functioning
- Use appropriate anatomical terminology to identify key body structures, body regions, and directions in the body
- Compare and contrast at least four medical imaging techniques in terms of their function and use in medicine

Though you may approach a course in anatomy and physiology strictly as a requirement for your field of study, the knowledge you gain in this course will serve you well in many aspects of your life. An understanding of anatomy and physiology is not only fundamental to any career in the health professions, but it can also benefit your own health. Familiarity with the human body can help you make healthful choices and prompt you to take appropriate action when signs of illness arise. Your knowledge in this field will help you understand news about nutrition, medications, medical devices, and procedures and help you understand genetic or infectious diseases. At some point, everyone will have a problem with some aspect of his or her body and your knowledge can help you to be a better parent, spouse, partner, friend, colleague, or caregiver.

This chapter begins with an overview of anatomy and physiology and a preview of the body regions and functions. It then covers the characteristics of life and how the body works to maintain stable conditions. It introduces a set of standard terms for body structures and for planes and positions in the body that will serve as a foundation for more comprehensive information

covered later in the text. It ends with examples of medical imaging used to see inside the living body.

Overview of Anatomy and Physiology

By the end of this section, you will be able to:

- Compare and contrast anatomy and physiology, including their specializations and methods of study
- Discuss the fundamental relationship between anatomy and physiology

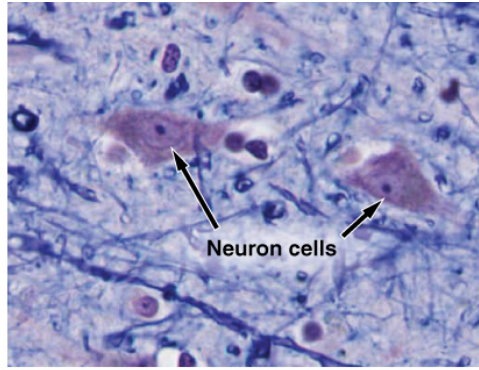
Human **anatomy** is the scientific study of the body's structures. Some of these structures are very small and can only be observed and analyzed with the assistance of a microscope. Other larger structures can readily be seen, manipulated, measured, and weighed. The word “anatomy” comes from a Greek root that means “to cut apart.” Human anatomy was first studied by observing the exterior of the body and observing the wounds of soldiers and other injuries. Later, physicians were allowed to dissect bodies of the dead to augment their knowledge. When a body is dissected, its structures are cut apart in order to observe their physical attributes and their relationships to one another. Dissection is still used in medical schools, anatomy courses, and in pathology labs. In order to observe structures in living people, however, a number of imaging techniques have been developed. These techniques allow clinicians to visualize structures inside the living body such as a cancerous tumor or a fractured bone.

Like most scientific disciplines, anatomy has areas of specialization. **Gross anatomy** is the study of the larger structures of the body, those visible without the aid of magnification ([\[link\]a](#)). Macro- means “large,” thus, gross anatomy is also referred to as macroscopic anatomy. In contrast, micro- means “small,” and **microscopic anatomy** is the study of structures that can be observed only with the use of a microscope or other magnification devices ([\[link\]b](#)). Microscopic anatomy includes cytology, the study of cells and histology, the study of tissues. As the technology of microscopes has advanced, anatomists have been able to observe smaller and smaller structures of the body, from slices of large structures like the heart, to the three-dimensional structures of large molecules in the body.

Gross and Microscopic Anatomy



(a)



(b)

(a) Gross anatomy considers large structures such as the brain. (b) Microscopic anatomy can deal with the same structures, though at a different scale. This is a micrograph of nerve cells from the brain. LM $\times 1600$. (credit a: "WriterHound"/Wikimedia Commons; credit b: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Anatomists take two general approaches to the study of the body's structures: regional and systemic. **Regional anatomy** is the study of the interrelationships of all of the structures in a specific body region, such as the abdomen. Studying regional anatomy helps us appreciate the interrelationships of body structures, such as how muscles, nerves, blood vessels, and other structures work together to serve a particular body region. In contrast, **systemic anatomy** is the study of the structures that make up a discrete body system—that is, a group of structures that work together to perform a unique body function. For example, a systemic anatomical study of the muscular system would consider all of the skeletal muscles of the body.

Whereas anatomy is about structure, physiology is about function. Human **physiology** is the scientific study of the chemistry and physics of the structures of the body and the ways in which they work together to support the functions of life. Much of the study of physiology centers on the body's tendency toward homeostasis. **Homeostasis** is the state of steady internal

conditions maintained by living things. The study of physiology certainly includes observation, both with the naked eye and with microscopes, as well as manipulations and measurements. However, current advances in physiology usually depend on carefully designed laboratory experiments that reveal the functions of the many structures and chemical compounds that make up the human body.

Like anatomists, physiologists typically specialize in a particular branch of physiology. For example, neurophysiology is the study of the brain, spinal cord, and nerves and how these work together to perform functions as complex and diverse as vision, movement, and thinking. Physiologists may work from the organ level (exploring, for example, what different parts of the brain do) to the molecular level (such as exploring how an electrochemical signal travels along nerves).

Form is closely related to function in all living things. For example, the thin flap of your eyelid can snap down to clear away dust particles and almost instantaneously slide back up to allow you to see again. At the microscopic level, the arrangement and function of the nerves and muscles that serve the eyelid allow for its quick action and retreat. At a smaller level of analysis, the function of these nerves and muscles likewise relies on the interactions of specific molecules and ions. Even the three-dimensional structure of certain molecules is essential to their function.

Your study of anatomy and physiology will make more sense if you continually relate the form of the structures you are studying to their function. In fact, it can be somewhat frustrating to attempt to study anatomy without an understanding of the physiology that a body structure supports. Imagine, for example, trying to appreciate the unique arrangement of the bones of the human hand if you had no conception of the function of the hand. Fortunately, your understanding of how the human hand manipulates tools—from pens to cell phones—helps you appreciate the unique alignment of the thumb in opposition to the four fingers, making your hand a structure that allows you to pinch and grasp objects and type text messages.

Chapter Review

Human anatomy is the scientific study of the body's structures. In the past, anatomy has primarily been studied via observing injuries, and later by the dissection of anatomical structures of cadavers, but in the past century, computer-assisted imaging techniques have allowed clinicians to look inside the living body. Human physiology is the scientific study of the chemistry and physics of the structures of the body. Physiology explains how the structures of the body work together to maintain life. It is difficult to study structure (anatomy) without knowledge of function (physiology). The two disciplines are typically studied together because form and function are closely related in all living things.

Review Questions

Exercise:

Problem:

Which of the following specialties might focus on studying all of the structures of the ankle and foot?

- a. microscopic anatomy
- b. muscle anatomy
- c. regional anatomy
- d. systemic anatomy

Solution:

C

Exercise:

Problem:

A scientist wants to study how the body uses foods and fluids during a marathon run. This scientist is most likely a(n) _____.

- a. exercise physiologist
- b. microscopic anatomist

- c. regional physiologist
 - d. systemic anatomist
-

Solution:

A

CRITICAL THINKING QUESTIONS

Exercise:

Problem:

Name at least three reasons to study anatomy and physiology.

Solution:

An understanding of anatomy and physiology is essential for any career in the health professions. It can also help you make choices that promote your health, respond appropriately to signs of illness, make sense of health-related news, and help you in your roles as a parent, spouse, partner, friend, colleague, and caregiver.

Exercise:

Problem:

For whom would an appreciation of the structural characteristics of the human heart come more easily: an alien who lands on Earth, abducts a human, and dissects his heart, or an anatomy and physiology student performing a dissection of the heart on her very first day of class? Why?

Solution:

A student would more readily appreciate the structures revealed in the dissection. Even though the student has not yet studied the workings of the heart and blood vessels in her class, she has experienced her heart

beating every moment of her life, has probably felt her pulse, and likely has at least a basic understanding of the role of the heart in pumping blood throughout her body. This understanding of the heart's function (physiology) would support her study of the heart's form (anatomy).

Glossary

anatomy

science that studies the form and composition of the body's structures

gross anatomy

study of the larger structures of the body, typically with the unaided eye; also referred to macroscopic anatomy

homeostasis

steady state of body systems that living organisms maintain

microscopic anatomy

study of very small structures of the body using magnification

physiology

science that studies the chemistry, biochemistry, and physics of the body's functions

regional anatomy

study of the structures that contribute to specific body regions

systemic anatomy

study of the structures that contribute to specific body systems

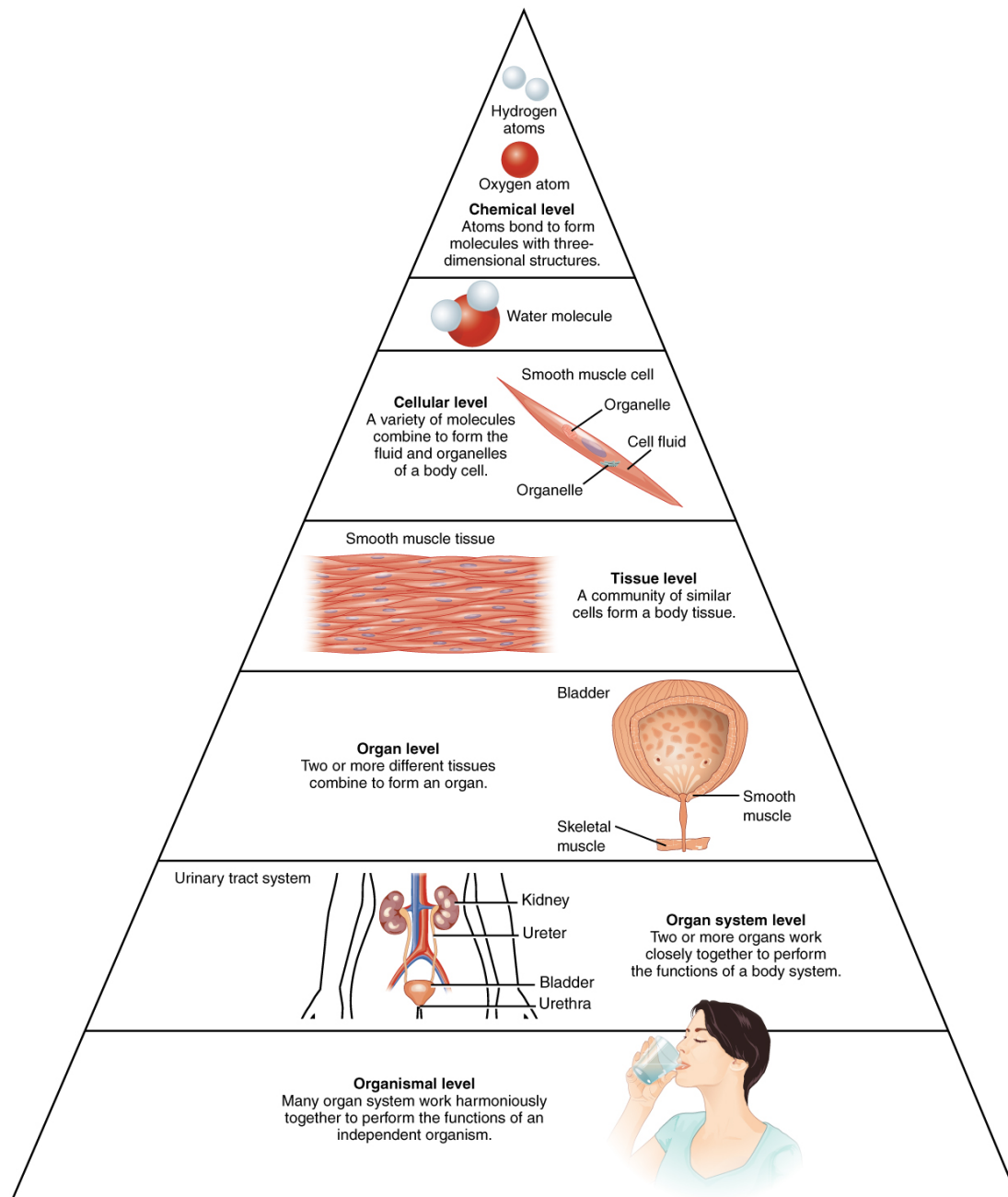
Structural Organization of the Human Body

By the end of this section, you will be able to:

- Describe the structure of the human body in terms of six levels of organization
- List the eleven organ systems of the human body and identify at least one organ and one major function of each

Before you begin to study the different structures and functions of the human body, it is helpful to consider its basic architecture; that is, how its smallest parts are assembled into larger structures. It is convenient to consider the structures of the body in terms of fundamental levels of organization that increase in complexity: subatomic particles, atoms, molecules, organelles, cells, tissues, organs, organ systems, organisms and biosphere ([\[link\]](#)).

Levels of Structural Organization of the Human Body



The organization of the body often is discussed in terms of six distinct levels of increasing complexity, from the smallest chemical building blocks to a unique human organism.

The Levels of Organization

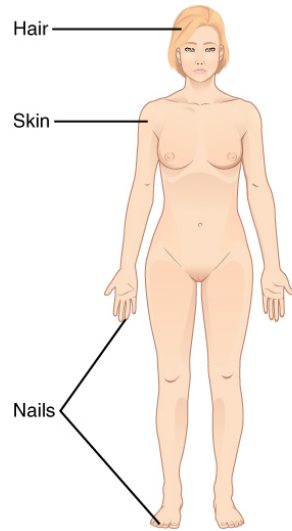
To study the chemical level of organization, scientists consider the simplest building blocks of matter: subatomic particles, atoms and molecules. All matter in the universe is composed of one or more unique pure substances called elements, familiar examples of which are hydrogen, oxygen, carbon, nitrogen, calcium, and iron. The smallest unit of any of these pure substances (elements) is an atom. Atoms are made up of subatomic particles such as the proton, electron and neutron. Two or more atoms combine to form a molecule, such as the water molecules, proteins, and sugars found in living things. Molecules are the chemical building blocks of all body structures.

A **cell** is the smallest independently functioning unit of a living organism. Even bacteria, which are extremely small, independently-living organisms, have a cellular structure. Each bacterium is a single cell. All living structures of human anatomy contain cells, and almost all functions of human physiology are performed in cells or are initiated by cells.

A human cell typically consists of flexible membranes that enclose cytoplasm, a water-based cellular fluid together with a variety of tiny functioning units called **organelles**. In humans, as in all organisms, cells perform all functions of life. A **tissue** is a group of many similar cells (though sometimes composed of a few related types) that work together to perform a specific function. An **organ** is an anatomically distinct structure of the body composed of two or more tissue types. Each organ performs one or more specific physiological functions. An **organ system** is a group of organs that work together to perform major functions or meet physiological needs of the body.

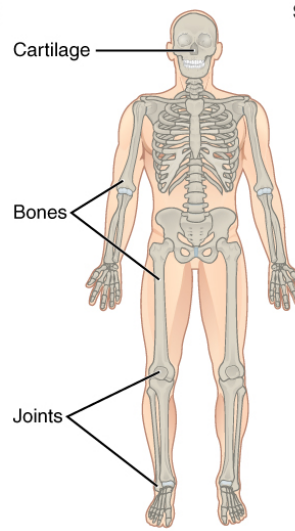
This book covers eleven distinct organ systems in the human body ([\[link\]](#) and [\[link\]](#)). Assigning organs to organ systems can be imprecise since organs that “belong” to one system can also have functions integral to another system. In fact, most organs contribute to more than one system.

Organ Systems of the Human Body



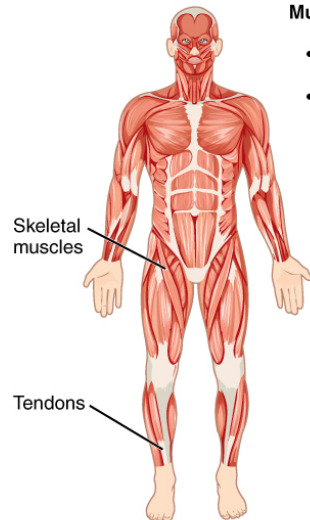
Integumentary System

- Encloses internal body structures
- Site of many sensory receptors



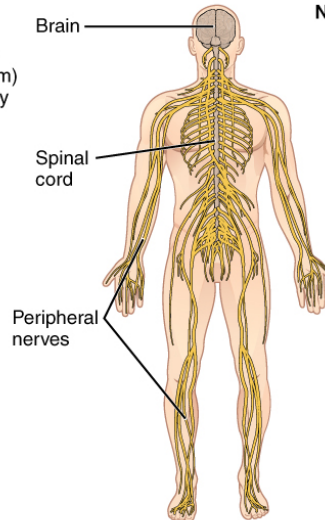
Skeletal System

- Supports the body
- Enables movement (with muscular system)



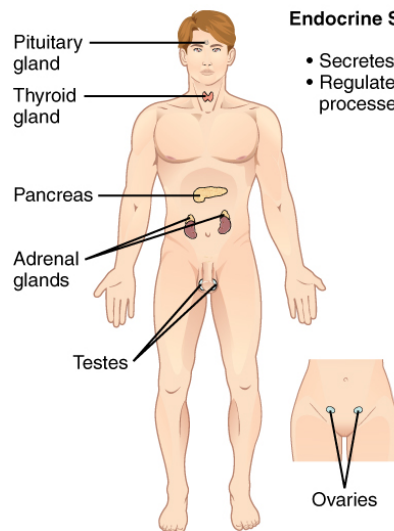
Muscular System

- Enables movement (with skeletal system)
- Helps maintain body temperature



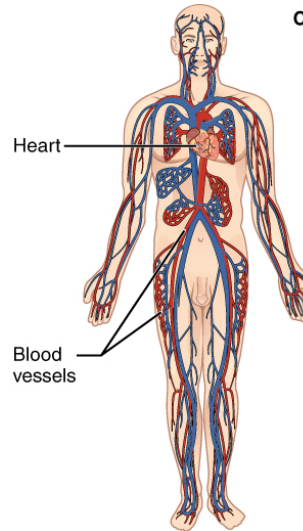
Nervous System

- Detects and processes sensory information
- Activates bodily responses



Endocrine System

- Secretes hormones
- Regulates bodily processes

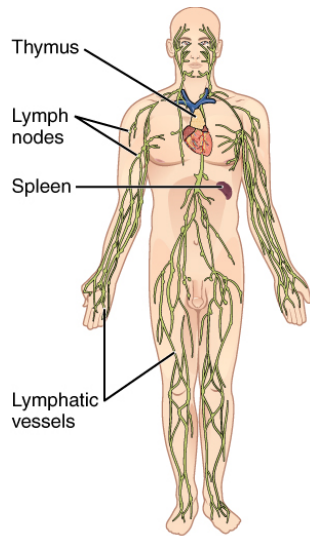


Cardiovascular System

- Delivers oxygen and nutrients to tissues
- Equalizes temperature in the body

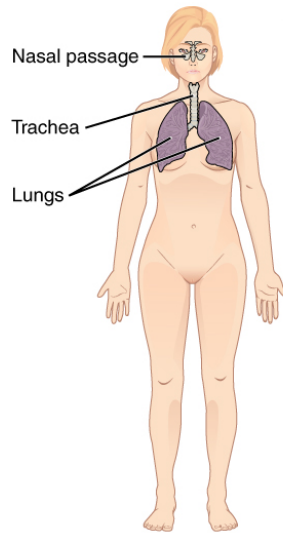
Organs that work together are grouped into organ systems.

Organ Systems of the Human Body (continued)



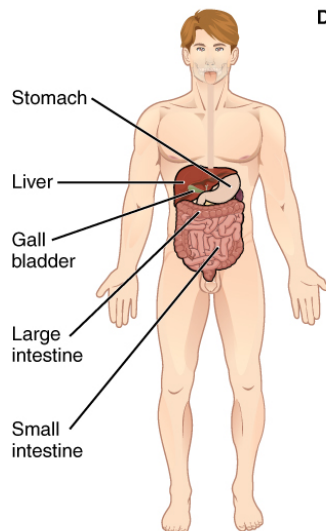
Lymphatic System

- Returns fluid to blood
- Defends against pathogens



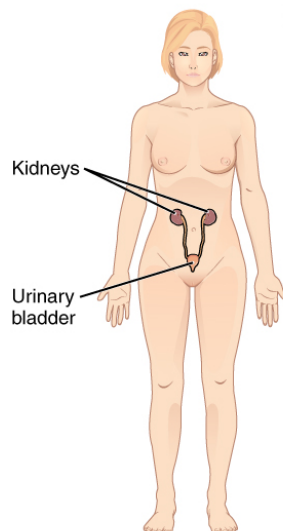
Respiratory System

- Removes carbon dioxide from the body
- Delivers oxygen to blood



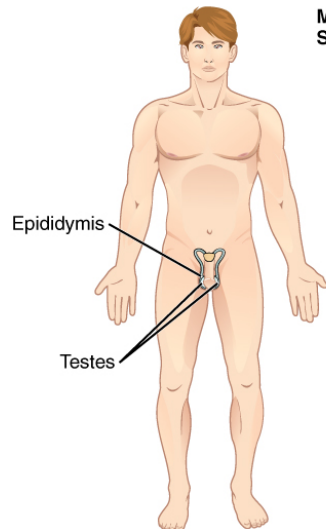
Digestive System

- Processes food for use by the body
- Removes wastes from undigested food



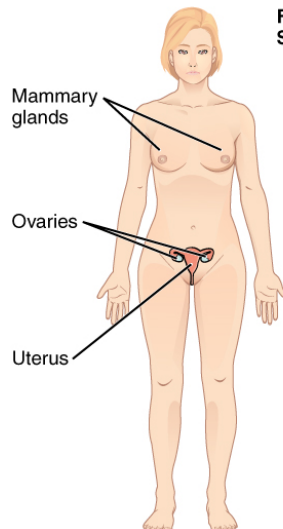
Urinary System

- Controls water balance in the body
- Removes wastes from blood and excretes them



Male Reproductive System

- Produces sex hormones and gametes
- Delivers gametes to female



Female Reproductive System

- Produces sex hormones and gametes
- Supports embryo/fetus until birth
- Produces milk for infant

Organs that work together are grouped into organ systems.

The organism level is the highest level of organization. An **organism** is a living being that has a cellular structure and that can independently perform all physiologic functions necessary for life. In multicellular organisms, including humans, all cells, tissues, organs, and organ systems of the body work together to maintain the life and health of the organism.

Chapter Review

Life processes of the human body are maintained at several levels of structural organization. These include the chemical, cellular, tissue, organ, organ system, and the organism level. Higher levels of organization are built from lower levels. Therefore, molecules combine to form cells, cells combine to form tissues, tissues combine to form organs, organs combine to form organ systems, and organ systems combine to form organisms.

Review Questions

Exercise:

Problem:

The smallest independently functioning unit of an organism is a(n) _____.

- a. cell
- b. molecule
- c. organ
- d. tissue

Solution:

A

Exercise:

Problem:

A collection of similar tissues that performs a specific function is an _____.

- a. organ
- b. organelle
- c. organism
- d. organ system

Solution:

A

Exercise:

Problem:

The body system responsible for structural support and movement is the _____.

- a. cardiovascular system
- b. endocrine system
- c. muscular system
- d. skeletal system

Solution:

D

CRITICAL THINKING QUESTIONS

Exercise:

Problem: Name the six levels of organization of the human body.

Solution:

Chemical, cellular, tissue, organ, organ system, organism.

Exercise:

Problem:

The female ovaries and the male testes are a part of which body system? Can these organs be members of more than one organ system? Why or why not?

Solution:

The female ovaries and the male testes are parts of the reproductive system. But they also secrete hormones, as does the endocrine system, therefore ovaries and testes function within both the endocrine and reproductive systems.

Glossary

cell

smallest independently functioning unit of all organisms; in animals, a cell contains cytoplasm, composed of fluid and organelles

organ

functionally distinct structure composed of two or more types of tissues

organ system

group of organs that work together to carry out a particular function

organism

living being that has a cellular structure and that can independently perform all physiologic functions necessary for life

tissue

group of similar or closely related cells that act together to perform a specific function

Functions of Human Life

By the end of this section, you will be able to:

- Explain the importance of organization to the function of the human organism
- Distinguish between metabolism, anabolism, and catabolism
- Provide at least two examples of human responsiveness and human movement
- Compare and contrast growth, differentiation, and reproduction

The different organ systems each have different functions and therefore unique roles to perform in physiology. These many functions can be summarized in terms of a few that we might consider definitive of human life: organization, metabolism, responsiveness, movement, development, and reproduction.

Organization

A human body consists of trillions of cells organized in a way that maintains distinct internal compartments. These compartments keep body cells separated from external environmental threats and keep the cells moist and nourished. They also separate internal body fluids from the countless microorganisms that grow on body surfaces, including the lining of certain tracts, or passageways. The intestinal tract, for example, is home to even more bacteria cells than the total of all human cells in the body, yet these bacteria are outside the body and cannot be allowed to circulate freely inside the body.

Cells, for example, have a cell membrane (also referred to as the plasma membrane) that keeps the intracellular environment—the fluids and organelles—separate from the extracellular environment. Blood vessels keep blood inside a closed circulatory system, and nerves and muscles are wrapped in connective tissue sheaths that separate them from surrounding structures. In the chest and abdomen, a variety of internal membranes keep major organs such as the lungs, heart, and kidneys separate from others.

The body's largest organ system is the integumentary system, which includes the skin and its associated structures, such as hair and nails. The surface tissue of skin is a barrier that protects internal structures and fluids from potentially harmful microorganisms and other toxins.

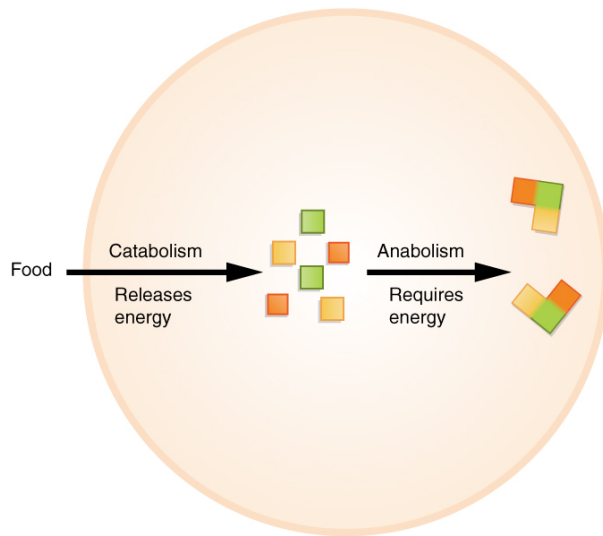
Metabolism

The first law of thermodynamics holds that energy can neither be created nor destroyed—it can only change form. Your basic function as an organism is to consume (ingest) energy and molecules in the foods you eat, convert some of it into fuel for movement, sustain your body functions, and build and maintain your body structures. There are two types of reactions that accomplish this: **anabolism** and **catabolism**.

- **Anabolism** is the process whereby smaller, simpler molecules are combined into larger, more complex substances. Your body can assemble, by utilizing energy, the complex chemicals it needs by combining small molecules derived from the foods you eat
- **Catabolism** is the process by which larger more complex substances are broken down into smaller simpler molecules. Catabolism releases energy. The complex molecules found in foods are broken down so the body can use their parts to assemble the structures and substances needed for life.

Taken together, these two processes are called metabolism. **Metabolism** is the sum of all anabolic and catabolic reactions that take place in the body ([\[link\]](#)). Both anabolism and catabolism occur simultaneously and continuously to keep you alive.

Metabolism



Anabolic reactions are building reactions, and they consume energy. Catabolic reactions break materials down and release energy. Metabolism includes both anabolic and catabolic reactions.

Every cell in your body makes use of a chemical compound, **adenosine triphosphate (ATP)**, to store and release energy. The cell stores energy in the synthesis (anabolism) of ATP, then moves the ATP molecules to the location where energy is needed to fuel cellular activities. Then the ATP is broken down (catabolism) and a controlled amount of energy is released, which is used by the cell to perform a particular job.

Note:



View this [animation](#) to learn more about metabolic processes. Which organs of the body likely carry out anabolic processes? What about catabolic processes?

Responsiveness

Responsiveness is the ability of an organism to adjust to changes in its internal and external environments. An example of responsiveness to external stimuli could include moving toward sources of food and water and away from perceived dangers. Changes in an organism's internal environment, such as increased body temperature, can cause the responses of sweating and the dilation of blood vessels in the skin in order to decrease body temperature, as shown by the runners in [\[link\]](#).

Movement

Human movement includes not only actions at the joints of the body, but also the motion of individual organs and even individual cells. As you read these words, red and white blood cells are moving throughout your body, muscle cells are contracting and relaxing to maintain your posture and to focus your vision, and glands are secreting chemicals to regulate body functions. Your body is coordinating the action of entire muscle groups to enable you to move air into and out of your lungs, to push blood throughout your body, and to propel the food you have eaten through your digestive tract. Consciously, of course, you contract your skeletal muscles to move the bones of your skeleton to get from one place to another (as the runners are doing in [\[link\]](#)), and to carry out all of the activities of your daily life.

Marathon Runners



Runners demonstrate two characteristics of living humans—responsiveness and movement. Anatomic structures and physiological processes allow runners to coordinate the action of muscle groups and sweat in response to rising internal body temperature. (credit: Phil Roeder/flickr)

Development, growth and reproduction

Development is all of the changes the body goes through in life. Development includes the process of **differentiation**, in which unspecialized cells become specialized in structure and function to perform certain tasks in the body. Development also includes the processes of growth and repair, both of which involve cell differentiation.

Growth is the increase in body size. Humans, like all multicellular organisms, grow by increasing the number of existing cells, increasing the amount of non-cellular material around cells (such as mineral deposits in bone), and, within very narrow limits, increasing the size of existing cells.

Reproduction is the formation of a new organism from parent organisms. In humans, reproduction is carried out by the male and female reproductive systems. Because death will come to all complex organisms, without reproduction, the line of organisms would end.

Chapter Review

Most processes that occur in the human body are not consciously controlled. They occur continuously to build, maintain, and sustain life. These processes include: organization, in terms of the maintenance of essential body boundaries; metabolism, including energy transfer via anabolic and catabolic reactions; responsiveness; movement; and growth, differentiation, reproduction, and renewal.

Interactive Link Questions

Exercise:

Problem:

View this [animation](#) to learn more about metabolic processes. What kind of catabolism occurs in the heart?

Solution:

Fatty acid catabolism.

Review Questions

Exercise:

Problem: Metabolism can be defined as the _____.

- a. adjustment by an organism to external or internal changes
- b. process whereby all unspecialized cells become specialized to perform distinct functions

- c. process whereby new cells are formed to replace worn-out cells
 - d. sum of all chemical reactions in an organism
-

Solution:

D

Exercise:

Problem:

Adenosine triphosphate (ATP) is an important molecule because it _____.

- a. is the result of catabolism
 - b. release energy in uncontrolled bursts
 - c. stores energy for use by body cells
 - d. All of the above
-

Solution:

C

Exercise:

Problem:

Cancer cells can be characterized as “generic” cells that perform no specialized body function. Thus cancer cells lack _____.

- a. differentiation
 - b. reproduction
 - c. responsiveness
 - d. both reproduction and responsiveness
-

Solution:

A

CRITICAL THINKING QUESTIONS

Exercise:

Problem:

Explain why the smell of smoke when you are sitting at a campfire does not trigger alarm, but the smell of smoke in your residence hall does.

Solution:

When you are sitting at a campfire, your sense of smell adapts to the smell of smoke. Only if that smell were to suddenly and dramatically intensify would you be likely to notice and respond. In contrast, the smell of even a trace of smoke would be new and highly unusual in your residence hall, and would be perceived as danger.

Exercise:

Problem:

Identify three different ways that growth can occur in the human body.

Solution:

Growth can occur by increasing the number of existing cells, increasing the size of existing cells, or increasing the amount of non-cellular material around cells.

Glossary

anabolism

assembly of more complex molecules from simpler molecules

catabolism

breaking down of more complex molecules into simpler molecules

development

changes an organism goes through during its life

differentiation

process by which unspecialized cells become specialized in structure and function

growth

process of increasing in size

metabolism

sum of all of the body's chemical reactions

renewal

process by which worn-out cells are replaced

reproduction

process by which new organisms are generated

responsiveness

ability of an organisms or a system to adjust to changes in conditions

Requirements for Human Life

By the end of this section, you will be able to:

- Discuss the role of oxygen and nutrients in maintaining human survival
- Explain why extreme heat and extreme cold threaten human survival
- Explain how the pressure exerted by gases and fluids influences human survival

Humans have been adapting to life on Earth for at least the past 200,000 years. Earth and its atmosphere have provided us with air to breathe, water to drink, and food to eat, but these are not the only requirements for survival. Although you may rarely think about it, you also cannot live outside of a certain range of temperature and pressure that the surface of our planet and its atmosphere provides. The next sections explore these four requirements of life.

Oxygen

Atmospheric air is only about 20 percent oxygen, but that oxygen is a key component of the chemical reactions that keep the body alive, including the reactions that produce ATP. Brain cells are especially sensitive to lack of oxygen because of their requirement for a high-and-steady production of ATP. Brain damage is likely within five minutes without oxygen, and death is likely within ten minutes.

Nutrients

A **nutrient** is a substance in foods and beverages that is essential to human survival. The three basic classes of nutrients are water, the energy-yielding and body-building nutrients, and the micronutrients (vitamins and minerals).

The most critical nutrient is water. Depending on the environmental temperature and our state of health, we may be able to survive for only a few days without water. The body's functional chemicals are dissolved and transported in water, and the chemical reactions of life take place in water.

Moreover, water is the largest component of cells, blood, and the fluid between cells, and water makes up about 70 percent of an adult's body mass. Water also helps regulate our internal temperature and cushions, protects, and lubricates joints and many other body structures.

The energy-yielding nutrients are primarily carbohydrates and lipids, while proteins mainly supply the amino acids that are the building blocks of the body itself. You ingest these in plant and animal foods and beverages, and the digestive system breaks them down into molecules small enough to be absorbed. The breakdown products of carbohydrates and lipids can then be used in the metabolic processes that convert them to ATP. Although you might feel as if you are starving after missing a single meal, you can survive without consuming the energy-yielding nutrients for at least several weeks.

Water and the energy-yielding nutrients are also referred to as macronutrients because the body needs them in large amounts. In contrast, micronutrients are vitamins and minerals. These elements and compounds participate in many essential chemical reactions and processes, such as nerve impulses, and some, such as calcium, also contribute to the body's structure. Your body can store some of the micronutrients in its tissues, and draw on those reserves if you fail to consume them in your diet for a few days or weeks. Some other micronutrients, such as vitamin C and most of the B vitamins, are water-soluble and cannot be stored, so you need to consume them every day or two.

Narrow Range of Temperature

You have probably seen news stories about athletes who died of heat stroke, or hikers who died of exposure to cold. Such deaths occur because the chemical reactions upon which the body depends can only take place within a narrow range of body temperature, from just below to just above 37°C (98.6°F). When body temperature rises well above or drops well below normal, certain proteins (enzymes) that facilitate chemical reactions lose their normal structure and their ability to function and the chemical reactions of metabolism cannot proceed.

That said, the body can respond effectively to short-term exposure to heat ([link](#)) or cold. One of the body's responses to heat is, of course, sweating. As sweat evaporates from skin, it removes some thermal energy from the body, cooling it. Adequate water (from the extracellular fluid in the body) is necessary to produce sweat, so adequate fluid intake is essential to balance that loss during the sweat response. Not surprisingly, the sweat response is much less effective in a humid environment because the air is already saturated with water. Thus, the sweat on the skin's surface is not able to evaporate, and internal body temperature can get dangerously high.

Extreme Heat



Humans adapt to some degree to repeated exposure to high temperatures. (credit: McKay Savage/flickr)

The body can also respond effectively to short-term exposure to cold. One response to cold is shivering, which is random muscle movement that generates heat. Another response is increased breakdown of stored energy to generate heat. When that energy reserve is depleted, however, and the core temperature begins to drop significantly, red blood cells will lose their ability to give up oxygen, denying the brain of this critical component of ATP production. This lack of oxygen can cause confusion, lethargy, and eventually loss of consciousness and death. The body responds to cold by

reducing blood circulation to the extremities, the hands and feet, in order to prevent blood from cooling there and so that the body's core can stay warm. Even when core body temperature remains stable, however, tissues exposed to severe cold, especially the fingers and toes, can develop frostbite when blood flow to the extremities has been much reduced. This form of tissue damage can be permanent and lead to gangrene, requiring amputation of the affected region.

Note:

Everyday Connection

Controlled Hypothermia

As you have learned, the body continuously engages in coordinated physiological processes to maintain a stable temperature. In some cases, however, overriding this system can be useful, or even life-saving.

Hypothermia is the clinical term for an abnormally low body temperature (hypo- = “below” or “under”). Controlled hypothermia is clinically induced hypothermia performed in order to reduce the metabolic rate of an organ or of a person's entire body.

Controlled hypothermia often is used, for example, during open-heart surgery because it decreases the metabolic needs of the brain, heart, and other organs, reducing the risk of damage to them. When controlled hypothermia is used clinically, the patient is given medication to prevent shivering. The body is then cooled to 25–32°C (79–89°F). The heart is stopped and an external heart-lung pump maintains circulation to the patient's body. The heart is cooled further and is maintained at a temperature below 15°C (60°F) for the duration of the surgery. This very cold temperature helps the heart muscle to tolerate its lack of blood supply during the surgery.

Some emergency department physicians use controlled hypothermia to reduce damage to the heart in patients who have suffered a cardiac arrest. In the emergency department, the physician induces coma and lowers the patient's body temperature to approximately 91 degrees. This condition, which is maintained for 24 hours, slows the patient's metabolic rate. Because the patient's organs require less blood to function, the heart's workload is reduced.

Narrow Range of Atmospheric Pressure

Pressure is a force exerted by a substance that is in contact with another substance. Atmospheric pressure is pressure exerted by the mixture of gases (primarily nitrogen and oxygen) in the Earth's atmosphere. Although you may not perceive it, atmospheric pressure is constantly pressing down on your body. This pressure keeps gases within your body, such as the gaseous nitrogen in body fluids, dissolved. If you were suddenly ejected from a space ship above Earth's atmosphere, you would go from a situation of normal pressure to one of very low pressure. The pressure of the nitrogen gas in your blood would be much higher than the pressure of nitrogen in the space surrounding your body. As a result, the nitrogen gas in your blood would expand, forming bubbles that could block blood vessels and even cause cells to break apart.

Atmospheric pressure does more than just keep blood gases dissolved. Your ability to breathe—that is, to take in oxygen and release carbon dioxide—also depends upon a precise atmospheric pressure. Altitude sickness occurs in part because the atmosphere at high altitudes exerts less pressure, reducing the exchange of these gases, and causing shortness of breath, confusion, headache, lethargy, and nausea. Mountain climbers carry oxygen to reduce the effects of both low oxygen levels and low barometric pressure at higher altitudes ([\[link\]](#)).

Harsh Conditions



Climbers on Mount Everest must

accommodate extreme cold, low oxygen levels, and low barometric pressure in an environment hostile to human life. (credit: Melanie Ko/flickr)

Note:

Homeostatic Imbalances

Decompression Sickness

Decompression sickness (DCS) is a condition in which gases dissolved in the blood or in other body tissues are no longer dissolved following a reduction in pressure on the body. This condition affects underwater divers who surface from a deep dive too quickly, and it can affect pilots flying at high altitudes in planes with unpressurized cabins. Divers often call this condition “the bends,” a reference to joint pain that is a symptom of DCS. In all cases, DCS is brought about by a reduction in barometric pressure. At high altitude, barometric pressure is much less than on Earth’s surface because pressure is produced by the weight of the column of air above the body pressing down on the body. The very great pressures on divers in deep water are likewise from the weight of a column of water pressing down on the body. For divers, DCS occurs at normal barometric pressure (at sea level), but it is brought on by the relatively rapid decrease of pressure as divers rise from the high pressure conditions of deep water to the now low, by comparison, pressure at sea level. Not surprisingly, diving in deep mountain lakes, where barometric pressure at the surface of the lake is less than that at sea level is more likely to result in DCS than diving in water at sea level.

In DCS, gases dissolved in the blood (primarily nitrogen) come rapidly out of solution, forming bubbles in the blood and in other body tissues. This occurs because when pressure of a gas over a liquid is decreased, the amount of gas that can remain dissolved in the liquid also is decreased. It is air pressure that keeps your normal blood gases dissolved in the blood. When pressure is reduced, less gas remains dissolved. You have seen this in effect when you open a carbonated drink. Removing the seal of the

bottle reduces the pressure of the gas over the liquid. This in turn causes bubbles as dissolved gases (in this case, carbon dioxide) come out of solution in the liquid.

The most common symptoms of DCS are pain in the joints, with headache and disturbances of vision occurring in 10 percent to 15 percent of cases. Left untreated, very severe DCS can result in death. Immediate treatment is with pure oxygen. The affected person is then moved into a hyperbaric chamber. A hyperbaric chamber is a reinforced, closed chamber that is pressurized to greater than atmospheric pressure. It treats DCS by repressurizing the body so that pressure can then be removed much more gradually. Because the hyperbaric chamber introduces oxygen to the body at high pressure, it increases the concentration of oxygen in the blood. This has the effect of replacing some of the nitrogen in the blood with oxygen, which is easier to tolerate out of solution.

The dynamic pressure of body fluids is also important to human survival. For example, blood pressure, which is the pressure exerted by blood as it flows within blood vessels, must be great enough to enable blood to reach all body tissues, and yet low enough to ensure that the delicate blood vessels can withstand the friction and force of the pulsating flow of pressurized blood.

Chapter Review

Humans cannot survive for more than a few minutes without oxygen, for more than several days without water, and for more than several weeks without carbohydrates, lipids, proteins, vitamins, and minerals. Although the body can respond to high temperatures by sweating and to low temperatures by shivering and increased fuel consumption, long-term exposure to extreme heat and cold is not compatible with survival. The body requires a precise atmospheric pressure to maintain its gases in solution and to facilitate respiration—the intake of oxygen and the release of carbon dioxide. Humans also require blood pressure high enough to ensure that blood reaches all body tissues but low enough to avoid damage to blood vessels.

Review Questions

Exercise:

Problem:

Humans have the most urgent need for a continuous supply of _____.

- a. food
- b. nitrogen
- c. oxygen
- d. water

Solution:

C

Exercise:

Problem: Which of the following statements about nutrients is true?

- a. All classes of nutrients are essential to human survival.
- b. Because the body cannot store any micronutrients, they need to be consumed nearly every day.
- c. Carbohydrates, lipids, and proteins are micronutrients.
- d. Macronutrients are vitamins and minerals.

Solution:

A

Exercise:

Problem:

C.J. is stuck in her car during a bitterly cold blizzard. Her body responds to the cold by _____.

- a. increasing the blood to her hands and feet
 - b. becoming lethargic to conserve heat
 - c. breaking down stored energy
 - d. significantly increasing blood oxygen levels
-

Solution:

C

CRITICAL THINKING QUESTIONS

Exercise:

Problem:

When you open a bottle of sparkling water, the carbon dioxide gas in the bottle form bubbles. If the bottle is left open, the water will eventually “go flat.” Explain these phenomena in terms of atmospheric pressure.

Solution:

In a sealed bottle of sparkling water, carbon dioxide gas is kept dissolved in the water under a very high pressure. When you open the bottle, the pressure of the gas above the liquid changes from artificially high to normal atmospheric pressure. The dissolved carbon dioxide gas expands, and rises in bubbles to the surface. When a bottle of sparkling water is left open, it eventually goes flat because its gases continue to move out of solution until the pressure in the water is approximately equal to atmospheric pressure.

Exercise:

Problem:

On his midsummer trek through the desert, Josh ran out of water. Why is this particularly dangerous?

Solution:

The primary way that the body responds to high environmental heat is by sweating; however, sweating requires water, which comes from body fluids, including blood plasma. If Josh becomes dehydrated, he will be unable to sweat adequately to cool his body, and he will be at risk for heat stroke as his blood pressure drops too much from the loss of water from the blood plasma.

Glossary

nutrient

chemical obtained from foods and beverages that is critical to human survival

pressure

force exerted by a substance in contact with another substance

Homeostasis

By the end of this section, you will be able to:

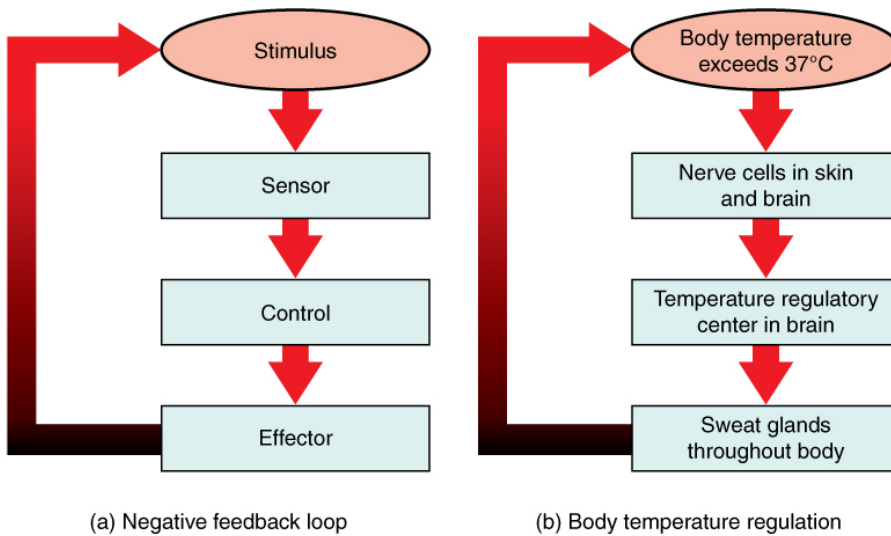
- Discuss the role of homeostasis in healthy functioning
- Contrast negative and positive feedback, giving one physiologic example of each mechanism

Maintaining homeostasis requires that the body continuously monitor its internal conditions. From body temperature to blood pressure to levels of certain nutrients, each physiological condition has a particular set point. A **set point** is the physiological value around which the normal range fluctuates. A **normal range** is the restricted set of values that is optimally healthful and stable. For example, the set point for normal human body temperature is approximately 37°C (98.6°F). Physiological parameters, such as body temperature and blood pressure, tend to fluctuate within a normal range a few degrees above and below that point. Control centers in the brain and other parts of the body monitor and react to deviations from homeostasis using negative feedback. **Negative feedback** is a mechanism that reverses a deviation from the set point. Therefore, negative feedback maintains body parameters within their normal range. The maintenance of homeostasis by negative feedback goes on throughout the body at all times, and an understanding of negative feedback is thus fundamental to an understanding of human physiology.

Negative Feedback

A negative feedback system has three basic components ([link](#)). A **sensor**, also referred to as a receptor, is a component of a feedback system that monitors a physiological value. This value is reported to the control center. The **control center** is the component in a feedback system that compares the value to the normal range. If the value deviates too much from the set point, then the control center activates an effector. An **effector** is the component in a feedback system that causes a change to reverse the situation and return the value to the normal range.

Negative Feedback Loop



In a negative feedback loop, a stimulus—a deviation from a set point—is resisted through a physiological process that returns the body to homeostasis. (a) A negative feedback loop has four basic parts. (b) Body temperature is regulated by negative feedback.

In order to set the system in motion, a stimulus must drive a physiological parameter beyond its normal range (that is, beyond homeostasis). This stimulus is “heard” by a specific sensor. For example, in the control of blood glucose, specific endocrine cells in the pancreas detect excess glucose (the stimulus) in the bloodstream. These pancreatic beta cells respond to the increased level of blood glucose by releasing the hormone insulin into the bloodstream. The insulin signals skeletal muscle fibers, fat cells (adipocytes), and liver cells to take up the excess glucose, removing it from the bloodstream. As glucose concentration in the bloodstream drops, the decrease in concentration—the actual negative feedback—is detected by pancreatic alpha cells, and insulin release stops. This prevents blood sugar levels from continuing to drop below the normal range.

Humans have a similar temperature regulation feedback system that works by promoting either heat loss or heat gain ([link](#) **b**). When the brain’s temperature regulation center receives data from the sensors indicating that

the body's temperature exceeds its normal range, it stimulates a cluster of brain cells referred to as the "heat-loss center." This stimulation has three major effects:

- Blood vessels in the skin begin to dilate allowing more blood from the body core to flow to the surface of the skin allowing the heat to radiate into the environment.
- As blood flow to the skin increases, sweat glands are activated to increase their output. As the sweat evaporates from the skin surface into the surrounding air, it takes heat with it.
- The depth of respiration increases, and a person may breathe through an open mouth instead of through the nasal passageways. This further increases heat loss from the lungs.

In contrast, activation of the brain's heat-gain center by exposure to cold reduces blood flow to the skin, and blood returning from the limbs is diverted into a network of deep veins. This arrangement traps heat closer to the body core and restricts heat loss. If heat loss is severe, the brain triggers an increase in random signals to skeletal muscles, causing them to contract and producing shivering. The muscle contractions of shivering release heat while using up ATP. The brain triggers the thyroid gland in the endocrine system to release thyroid hormone, which increases metabolic activity and heat production in cells throughout the body. The brain also signals the adrenal glands to release epinephrine (adrenaline), a hormone that causes the breakdown of glycogen into glucose, which can be used as an energy source. The breakdown of glycogen into glucose also results in increased metabolism and heat production.

Note:



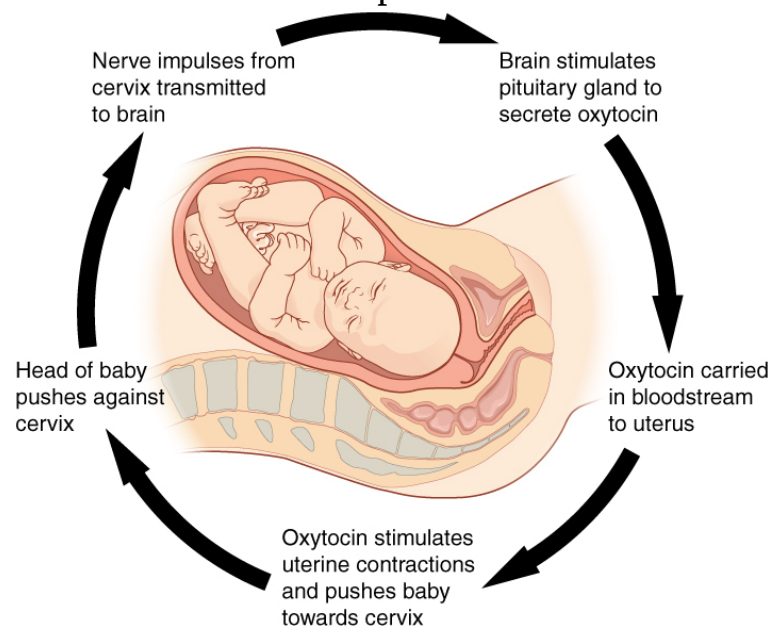
Water concentration in the body is critical for proper functioning. A person's body retains very tight control on water levels without conscious control by the person. Watch this [video](#) to learn more about water concentration in the body. Which organ has primary control over the amount of water in the body?

Positive Feedback

Positive feedback intensifies a change in the body's physiological condition rather than reversing it. A deviation from the normal range results in more change, and the system moves farther away from the normal range. Positive feedback in the body is normal only when there is a definite end point. Childbirth and the body's response to blood loss are two examples of positive feedback loops that are normal but are activated only when needed.

Childbirth at full term is an example of a situation in which the maintenance of the existing body state is not desired. Enormous changes in the mother's body are required to expel the baby at the end of pregnancy. And the events of childbirth, once begun, must progress rapidly to a conclusion or the life of the mother and the baby are at risk. The extreme muscular work of labor and delivery are the result of a positive feedback system ([link](#)).

Positive Feedback Loop



Normal childbirth is driven by a positive feedback loop. A positive feedback loop results in a change in the body's status, rather than a return to homeostasis.

The first contractions of labor (the stimulus) push the baby toward the cervix (the lowest part of the uterus). The cervix contains stretch-sensitive nerve cells that monitor the degree of stretching (the sensors). These nerve cells send messages to the brain, which in turn causes the pituitary gland at the base of the brain to release the hormone oxytocin into the bloodstream. Oxytocin causes stronger contractions of the smooth muscles in of the uterus (the effectors), pushing the baby further down the birth canal. This causes even greater stretching of the cervix. The cycle of stretching, oxytocin release, and increasingly more forceful contractions stops only when the baby is born. At this point, the stretching of the cervix halts, stopping the release of oxytocin.

A second example of positive feedback centers on reversing extreme damage to the body. Following a penetrating wound, the most immediate threat is excessive blood loss. Less blood circulating means reduced blood pressure and reduced perfusion (penetration of blood) to the brain and other vital organs. If perfusion is severely reduced, vital organs will shut down and the person will die. The body responds to this potential catastrophe by releasing substances in the injured blood vessel wall that begin the process of blood clotting. As each step of clotting occurs, it stimulates the release of more clotting substances. This accelerates the processes of clotting and sealing off the damaged area. Clotting is contained in a local area based on the tightly controlled availability of clotting proteins. This is an adaptive, life-saving cascade of events.

Chapter Review

Homeostasis is the activity of cells throughout the body to maintain the physiological state within a narrow range that is compatible with life.

Homeostasis is regulated by negative feedback loops and, much less frequently, by positive feedback loops. Both have the same components of a stimulus, sensor, control center, and effector; however, negative feedback loops work to prevent an excessive response to the stimulus, whereas positive feedback loops intensify the response until an end point is reached.

Interactive Link Questions

Exercise:

Problem:

Water concentration in the body is critical for proper functioning. A person's body retains very tight control on water levels without conscious control by the person. Watch this [video](#) to learn more about water concentration in the body. Which organ has primary control over the amount of water in the body?

Solution:

The kidneys.

Review Questions

Exercise:

Problem:

After you eat lunch, nerve cells in your stomach respond to the distension (the stimulus) resulting from the food. They relay this information to _____.

- a. a control center
- b. a set point
- c. effectors
- d. sensors

Solution:

A

Exercise:

Problem: Stimulation of the heat-loss center causes _____.

- a. blood vessels in the skin to constrict
- b. breathing to become slow and shallow
- c. sweat glands to increase their output
- d. All of the above

Solution:

C

Exercise:

Problem:

Which of the following is an example of a normal physiologic process that uses a positive feedback loop?

- a. blood pressure regulation
- b. childbirth
- c. regulation of fluid balance
- d. temperature regulation

Solution:

B

Critical Thinking Questions

Exercise:

Problem:

Identify the four components of a negative feedback loop and explain what would happen if secretion of a body chemical controlled by a negative feedback system became too great.

Solution:

The four components of a negative feedback loop are: stimulus, sensor, control center, and effector. If too great a quantity of the chemical were excreted, sensors would activate a control center, which would in turn activate an effector. In this case, the effector (the secreting cells) would be adjusted downward.

Exercise:**Problem:**

What regulatory processes would your body use if you were trapped by a blizzard in an unheated, uninsulated cabin in the woods?

Solution:

Any prolonged exposure to extreme cold would activate the brain's heat-gain center. This would reduce blood flow to your skin, and shunt blood returning from your limbs away from the digits and into a network of deep veins. Your brain's heat-gain center would also increase your muscle contraction, causing you to shiver. This increases the energy consumption of skeletal muscle and generates more heat. Your body would also produce thyroid hormone and epinephrine, chemicals that promote increased metabolism and heat production.

Glossary

control center

compares values to their normal range; deviations cause the activation of an effector

effector

organ that can cause a change in a value

negative feedback

homeostatic mechanism that tends to stabilize an upset in the body's physiological condition by preventing an excessive response to a stimulus, typically as the stimulus is removed

normal range

range of values around the set point that do not cause a reaction by the control center

positive feedback

mechanism that intensifies a change in the body's physiological condition in response to a stimulus

sensor

(also, receptor) reports a monitored physiological value to the control center

set point

ideal value for a physiological parameter; the level or small range within which a physiological parameter such as blood pressure is stable and optimally healthful, that is, within its parameters of homeostasis

Anatomical Terminology

By the end of this section, you will be able to:

- Demonstrate the anatomical position
- Describe the human body using directional and regional terms
- Identify three planes most commonly used in the study of anatomy
- Distinguish between the posterior (dorsal) and the anterior (ventral) body cavities, identifying their subdivisions and representative organs found in each
- Describe serous membrane and explain its function

Anatomists and health care providers use terminology that can be bewildering to the uninitiated. However, the purpose of this language is not to confuse, but rather to increase precision and reduce medical errors. For example, is a scar “above the wrist” located on the forearm two or three inches away from the hand? Or is it at the base of the hand? Is it on the palm-side or back-side? By using precise anatomical terminology, we eliminate ambiguity. Anatomical terms derive from ancient Greek and Latin words. Because these languages are no longer used in everyday conversation, the meaning of their words does not change.

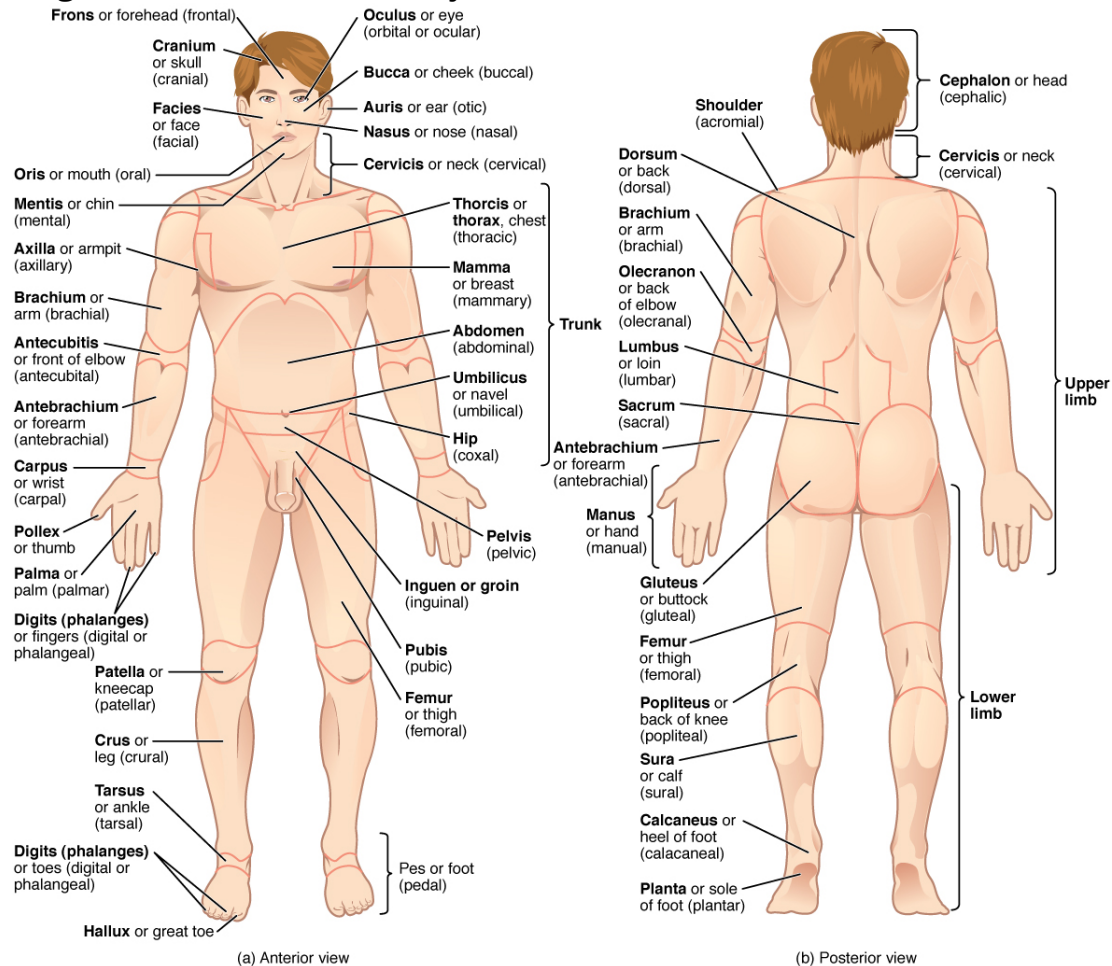
Anatomical terms are made up of roots, prefixes, and suffixes. The root of a term often refers to an organ, tissue, or condition, whereas the prefix or suffix often describes the root. For example, in the disorder hypertension, the prefix “hyper-” means “high” or “over,” and the root word “tension” refers to pressure, so the word “hypertension” refers to abnormally high blood pressure.

Anatomical Position

To further increase precision, anatomists standardize the way in which they view the body. Just as maps are normally oriented with north at the top, the standard body “map,” or **anatomical position**, is that of the body standing upright, with the feet at shoulder width and parallel, toes forward. The upper limbs are held out to each side, and the palms of the hands face forward as illustrated in [\[link\]](#). Using this standard position reduces confusion. It does not matter how the body being described is oriented, the

terms are used as if it is in anatomical position. For example, a scar in the “anterior (front) carpal (wrist) region” would be present on the palm side of the wrist. The term “anterior” would be used even if the hand were palm down on a table.

Regions of the Human Body



The human body is shown in anatomical position in an (a) anterior view and a (b) posterior view. The regions of the body are labeled in boldface.

A body that is lying down is described as either prone or supine. **Prone** describes a face-down orientation, and **supine** describes a face up orientation. These terms are sometimes used in describing the position of the body during specific physical examinations or surgical procedures.

Regional Terms

The human body's numerous regions have specific terms to help increase precision (see [\[link\]](#)). Notice that the term "brachium" or "arm" is reserved for the "upper arm" and "antebrachium" or "forearm" is used rather than "lower arm." Similarly, "femur" or "thigh" is correct, and "leg" or "crus" is reserved for the portion of the lower limb between the knee and the ankle. You will be able to describe the body's regions using the terms from the figure.

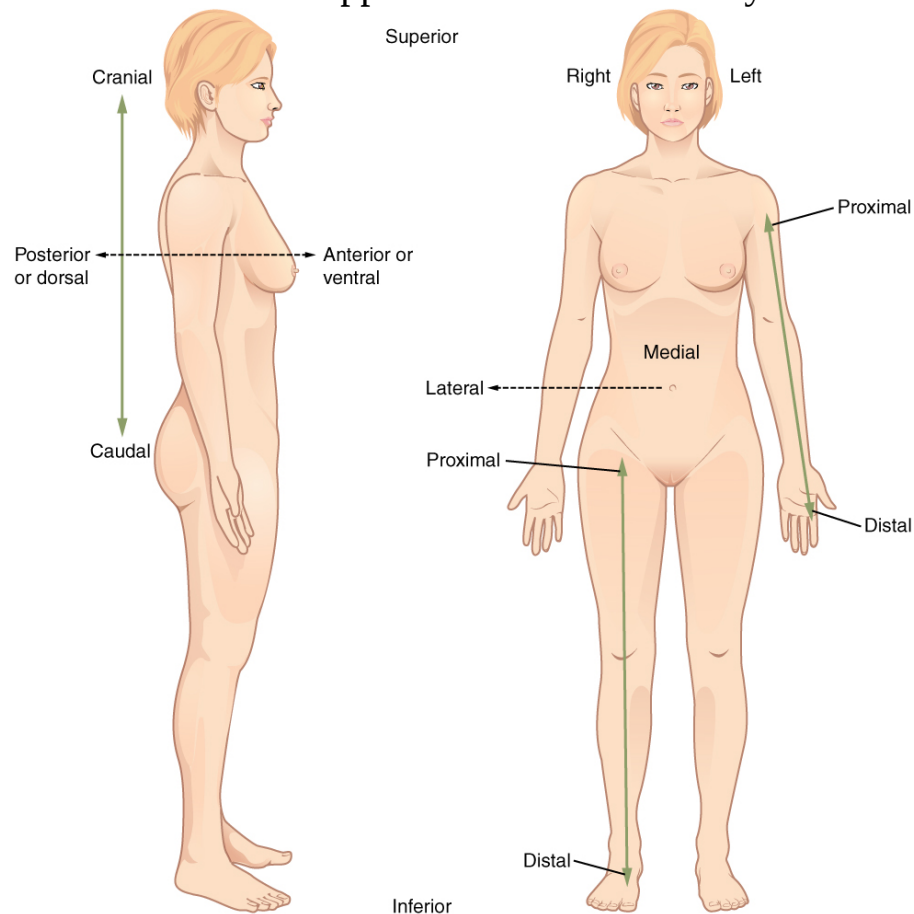
Directional Terms

Certain directional anatomical terms appear throughout this and any other anatomy textbook ([\[link\]](#)). These terms are essential for describing the relative locations of different body structures. For instance, an anatomist might describe one band of tissue as "inferior to" another or a physician might describe a tumor as "superficial to" a deeper body structure. Commit these terms to memory to avoid confusion when you are studying or describing the locations of particular body parts.

- **Anterior** (or **ventral**) Describes the front or direction toward the front of the body. The toes are anterior to the foot.
- **Posterior** (or **dorsal**) Describes the back or direction toward the back of the body. The popliteus is posterior to the patella.
- **Superior** (or **cranial**) describes a position above or higher than another part of the body proper. The orbits are superior to the oris.
- **Inferior** (or **caudal**) describes a position below or lower than another part of the body proper; near or toward the tail (in humans, the coccyx, or lowest part of the spinal column). The pelvis is inferior to the abdomen.
- **Lateral** describes the side or direction toward the side of the body. The thumb (pollex) is lateral to the digits.
- **Medial** describes the middle or direction toward the middle of the body. The hallux is the medial toe.
- **Proximal** describes a position in a limb that is nearer to the point of attachment or the trunk of the body. The brachium is proximal to the antebrachium.

- **Distal** describes a position in a limb that is farther from the point of attachment or the trunk of the body. The crus is distal to the femur.
- **Superficial** describes a position closer to the surface of the body. The skin is superficial to the bones.
- **Deep** describes a position farther from the surface of the body. The brain is deep to the skull.

Directional Terms Applied to the Human Body



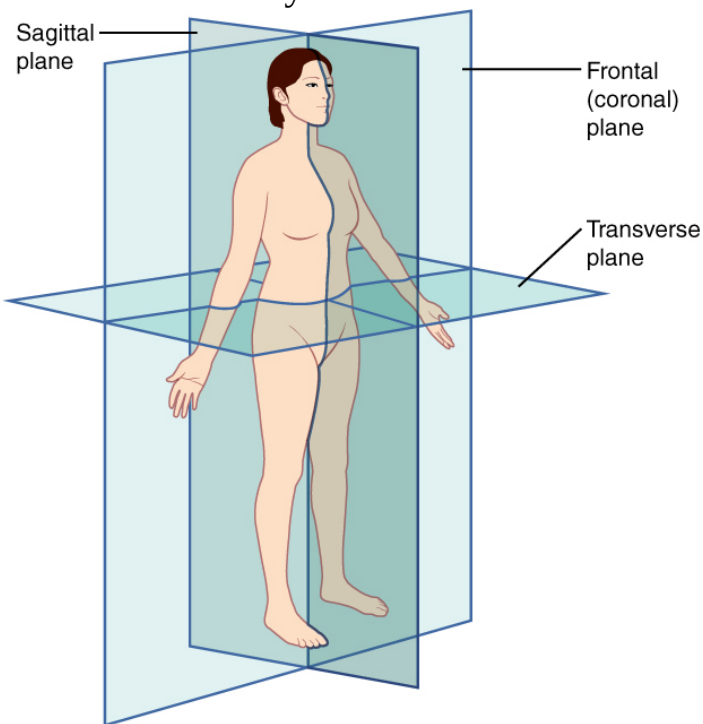
Paired directional terms are shown as applied to the human body.

Body Planes

A **section** is a two-dimensional surface of a three-dimensional structure that has been cut. Modern medical imaging devices enable clinicians to obtain “virtual sections” of living bodies. We call these scans. Body sections and scans can be correctly interpreted, however, only if the viewer understands the plane along which the section was made. A **plane** is an imaginary two-dimensional surface that passes through the body. There are three planes commonly referred to in anatomy and medicine, as illustrated in [\[link\]](#).

- The **sagittal plane** is the plane that divides the body or an organ vertically into right and left sides. If this vertical plane runs directly down the middle of the body, it is called the midsagittal or median plane. If it divides the body into unequal right and left sides, it is called a parasagittal plane or less commonly a longitudinal section.
- The **frontal plane** is the plane that divides the body or an organ into an anterior (front) portion and a posterior (rear) portion. The frontal plane is often referred to as a coronal plane. (“Corona” is Latin for “crown.”)
- The **transverse plane** is the plane that divides the body or organ horizontally into upper and lower portions. Transverse planes produce images referred to as cross sections.

Planes of the Body

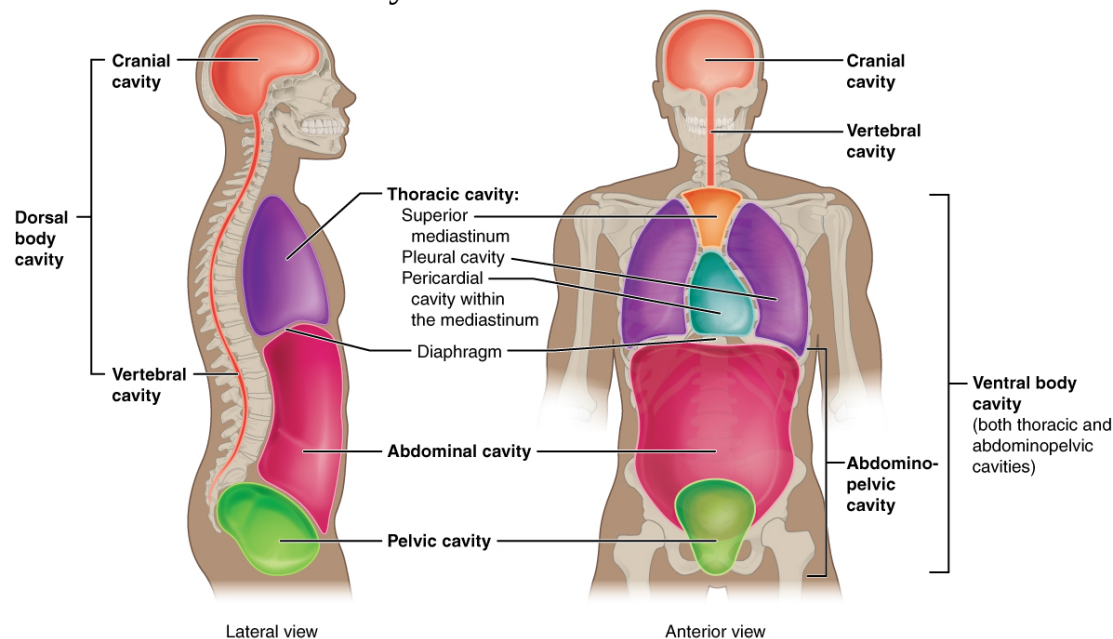


The three planes most commonly used in anatomical and medical imaging are the sagittal, frontal (or coronal), and transverse plane.

Body Cavities and Serous Membranes

The body maintains its internal organization by means of membranes, sheaths, and other structures that separate compartments. The **dorsal (posterior) cavity** and the **ventral (anterior) cavity** are the largest body compartments ([\[link\]](#)). These cavities contain and protect delicate internal organs, and the ventral cavity allows for significant changes in the size and shape of the organs as they perform their functions. The lungs, heart, stomach, and intestines, for example, can expand and contract without distorting other tissues or disrupting the activity of nearby organs.

Dorsal and Ventral Body Cavities



The ventral cavity includes the thoracic and abdominopelvic cavities and their subdivisions. The dorsal cavity includes the cranial and spinal cavities.

Subdivisions of the Posterior (Dorsal) and Anterior (Ventral) Cavities

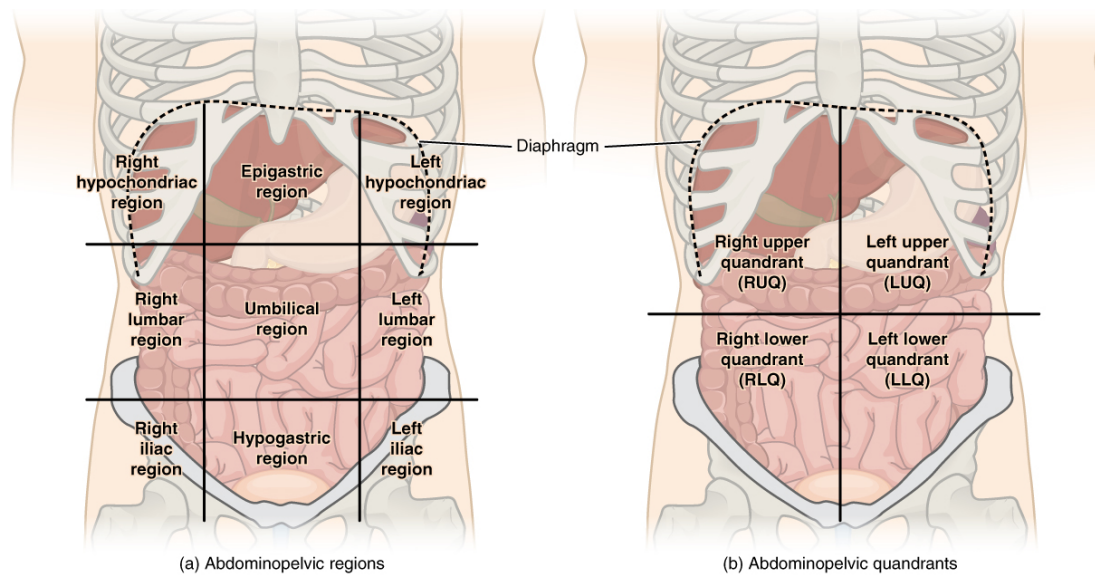
The posterior (dorsal) and anterior (ventral) cavities are each subdivided into smaller cavities. In the posterior (dorsal) cavity, the **cranial cavity** houses the brain, and the **spinal cavity** (or vertebral cavity) encloses the spinal cord. Just as the brain and spinal cord make up a continuous, uninterrupted structure, the cranial and spinal cavities that house them are also continuous. The brain and spinal cord are protected by the bones of the skull and vertebral column and by cerebrospinal fluid, a colorless fluid produced by the brain, which cushions the brain and spinal cord within the posterior (dorsal) cavity.

The anterior (ventral) cavity has two main subdivisions: the thoracic cavity and the abdominopelvic cavity (see [\[link\]](#)). The **thoracic cavity** is the more superior subdivision of the anterior cavity, and it is enclosed by the rib cage. The thoracic cavity contains the lungs and the heart, which is located in the mediastinum. The diaphragm forms the floor of the thoracic cavity and separates it from the more inferior abdominopelvic cavity. The **abdominopelvic cavity** is the largest cavity in the body. Although no membrane physically divides the abdominopelvic cavity, it can be useful to distinguish between the abdominal cavity, the division that houses the digestive organs, and the pelvic cavity, the division that houses the organs of reproduction.

Abdominal Regions and Quadrants

To promote clear communication, for instance about the location of a patient's abdominal pain or a suspicious mass, health care providers typically divide up the cavity into either nine regions or four quadrants ([\[link\]](#)).

Regions and Quadrants of the Peritoneal Cavity

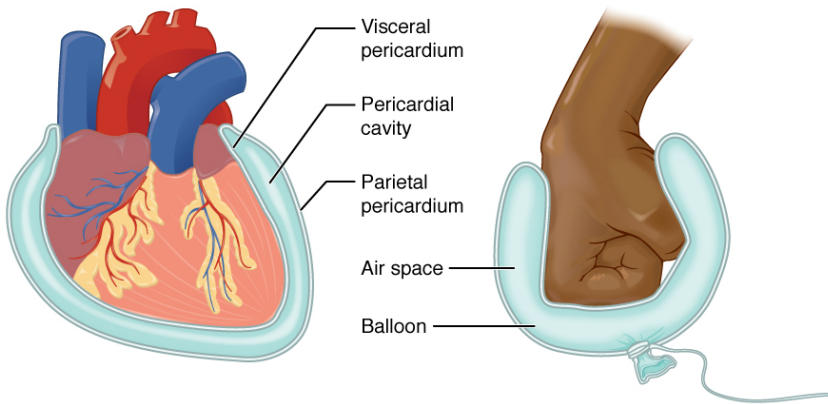


There are (a) nine abdominal regions and (b) four abdominal quadrants in the peritoneal cavity.

The more detailed regional approach subdivides the cavity with one horizontal line immediately inferior to the ribs and one immediately superior to the pelvis, and two vertical lines drawn as if dropped from the midpoint of each clavicle (collarbone). There are nine resulting regions. The simpler quadrants approach, which is more commonly used in medicine, subdivides the cavity with one horizontal and one vertical line that intersect at the patient's umbilicus (navel).

Membranes of the Anterior (Ventral) Body Cavity

A **serous membrane** (also referred to a serosa) is one of the thin membranes that cover the walls and organs in the thoracic and abdominopelvic cavities. The parietal layers of the membranes line the walls of the body cavity (pariet- refers to a cavity wall). The visceral layer of the membrane covers the organs (the viscera). Between the parietal and visceral layers is a very thin, fluid-filled serous space, or cavity ([link](#)).
Serous Membrane



Serous membrane lines the pericardial cavity and reflects back to cover the heart—much the same way that an underinflated balloon would form two layers surrounding a fist.

There are three serous cavities and their associated membranes. The **pleura** is the serous membrane that encloses the pleural cavity; the pleural cavity surrounds the lungs. The **pericardium** is the serous membrane that encloses the pericardial cavity; the pericardial cavity surrounds the heart. The **peritoneum** is the serous membrane that encloses the peritoneal cavity; the peritoneal cavity surrounds several organs in the abdominopelvic cavity. The serous membranes form fluid-filled sacs, or cavities, that are meant to cushion and reduce friction on internal organs when they move, such as when the lungs inflate or the heart beats. Both the parietal and visceral serosa secrete the thin, slippery serous fluid located within the serous cavities. The pleural cavity reduces friction between the lungs and the body wall. Likewise, the pericardial cavity reduces friction between the heart and the wall of the pericardium. The peritoneal cavity reduces friction between the abdominal and pelvic organs and the body wall. Therefore, serous membranes provide additional protection to the viscera they enclose by reducing friction that could lead to inflammation of the organs.

Chapter Review

Ancient Greek and Latin words are used to build anatomical terms. A standard reference position for mapping the body's structures is the normal anatomical position. Regions of the body are identified using terms such as "occipital" that are more precise than common words and phrases such as "the back of the head." Directional terms such as anterior and posterior are essential for accurately describing the relative locations of body structures. Images of the body's interior commonly align along one of three planes: the sagittal, frontal, or transverse. The body's organs are organized in one of two main cavities—dorsal (also referred to posterior) and ventral (also referred to anterior)—which are further sub-divided according to the structures present in each area. The serous membranes have two layers—parietal and visceral—surrounding a fluid filled space. Serous membranes cover the lungs (pleural serosa), heart (pericardial serosa), and some abdominopelvic organs (peritoneal serosa).

Review Chapter

Exercise:

Problem:

What is the position of the body when it is in the "normal anatomical position?"

- a. The person is prone with upper limbs, including palms, touching sides and lower limbs touching at sides.
- b. The person is standing facing the observer, with upper limbs extended out at a ninety-degree angle from the torso and lower limbs in a wide stance with feet pointing laterally
- c. The person is supine with upper limbs, including palms, touching sides and lower limbs touching at sides.
- d. None of the above

Solution:

D

Exercise:

Problem:

To make a banana split, you halve a banana into two long, thin, right and left sides along the _____.

- a. coronal plane
- b. longitudinal plane
- c. midsagittal plane
- d. transverse plane

Solution:

C

Exercise:

Problem: The lumbar region is _____.

- a. inferior to the gluteal region
- b. inferior to the umbilical region
- c. superior to the cervical region
- d. superior to the popliteal region

Solution:

D

Exercise:

Problem: The heart is within the _____.

- a. cranial cavity
- b. mediastinum
- c. posterior (dorsal) cavity
- d. All of the above

Solution:

B

Critical Thinking Question**Exercise:****Problem:**

In which direction would an MRI scanner move to produce sequential images of the body in the frontal plane, and in which direction would an MRI scanner move to produce sequential images of the body in the sagittal plane?

Solution:

If the body were supine or prone, the MRI scanner would move from top to bottom to produce frontal sections, which would divide the body into anterior and posterior portions, as in “cutting” a deck of cards. Again, if the body were supine or prone, to produce sagittal sections, the scanner would move from left to right or from right to left to divide the body lengthwise into left and right portions.

Exercise:**Problem:**

If a bullet were to penetrate a lung, which three anterior thoracic body cavities would it enter, and which layer of the serous membrane would it encounter first?

Solution:

The bullet would enter the ventral, thoracic, and pleural cavities, and it would encounter the parietal layer of serous membrane first.

Glossary

abdominopelvic cavity

division of the anterior (ventral) cavity that houses the abdominal and pelvic viscera

anatomical position

standard reference position used for describing locations and directions on the human body

anterior

describes the front or direction toward the front of the body; also referred to as ventral

anterior cavity

larger body cavity located anterior to the posterior (dorsal) body cavity; includes the serous membrane-lined pleural cavities for the lungs, pericardial cavity for the heart, and peritoneal cavity for the abdominal and pelvic organs; also referred to as ventral cavity

caudal

describes a position below or lower than another part of the body proper; near or toward the tail (in humans, the coccyx, or lowest part of the spinal column); also referred to as inferior

cranial

describes a position above or higher than another part of the body proper; also referred to as superior

cranial cavity

division of the posterior (dorsal) cavity that houses the brain

deep

describes a position farther from the surface of the body

distal

describes a position farther from the point of attachment or the trunk of the body

dorsal

describes the back or direction toward the back of the body; also referred to as posterior

dorsal cavity

posterior body cavity that houses the brain and spinal cord; also referred to as the posterior body cavity

frontal plane

two-dimensional, vertical plane that divides the body or organ into anterior and posterior portions

inferior

describes a position below or lower than another part of the body proper; near or toward the tail (in humans, the coccyx, or lowest part of the spinal column); also referred to as caudal

lateral

describes the side or direction toward the side of the body

medial

describes the middle or direction toward the middle of the body

pericardium

sac that encloses the heart

peritoneum

serous membrane that lines the abdominopelvic cavity and covers the organs found there

plane

imaginary two-dimensional surface that passes through the body

pleura

serous membrane that lines the pleural cavity and covers the lungs

posterior

describes the back or direction toward the back of the body; also referred to as dorsal

posterior cavity

posterior body cavity that houses the brain and spinal cord; also referred to as dorsal cavity

prone

face down

proximal

describes a position nearer to the point of attachment or the trunk of the body

sagittal plane

two-dimensional, vertical plane that divides the body or organ into right and left sides

section

in anatomy, a single flat surface of a three-dimensional structure that has been cut through

serous membrane

membrane that covers organs and reduces friction; also referred to as serosa

serosa

membrane that covers organs and reduces friction; also referred to as serous membrane

spinal cavity

division of the dorsal cavity that houses the spinal cord; also referred to as vertebral cavity

superficial

describes a position nearer to the surface of the body

superior

describes a position above or higher than another part of the body proper; also referred to as cranial

supine
face up

thoracic cavity
division of the anterior (ventral) cavity that houses the heart, lungs, esophagus, and trachea

transverse plane
two-dimensional, horizontal plane that divides the body or organ into superior and inferior portions

ventral
describes the front or direction toward the front of the body; also referred to as anterior

ventral cavity
larger body cavity located anterior to the posterior (dorsal) body cavity; includes the serous membrane-lined pleural cavities for the lungs, pericardial cavity for the heart, and peritoneal cavity for the abdominal and pelvic organs; also referred to as anterior body cavity

Medical Imaging

By the end of this section, you will be able to:

- Discuss the uses and drawbacks of X-ray imaging
- Identify four modern medical imaging techniques and how they are used

For thousands of years, fear of the dead and legal sanctions limited the ability of anatomists and physicians to study the internal structures of the human body. An inability to control bleeding, infection, and pain made surgeries infrequent, and those that were performed—such as wound suturing, amputations, tooth and tumor removals, skull drilling, and cesarean births—did not greatly advance knowledge about internal anatomy. Theories about the function of the body and about disease were therefore largely based on external observations and imagination. During the fourteenth and fifteenth centuries, however, the detailed anatomical drawings of Italian artist and anatomist Leonardo da Vinci and Flemish anatomist Andreas Vesalius were published, and interest in human anatomy began to increase. Medical schools began to teach anatomy using human dissection; although some resorted to grave robbing to obtain corpses. Laws were eventually passed that enabled students to dissect the corpses of criminals and those who donated their bodies for research. Still, it was not until the late nineteenth century that medical researchers discovered non-surgical methods to look inside the living body.

X-Rays

German physicist Wilhelm Röntgen (1845–1923) was experimenting with electrical current when he discovered that a mysterious and invisible “ray” would pass through his flesh but leave an outline of his bones on a screen coated with a metal compound. In 1895, Röntgen made the first durable record of the internal parts of a living human: an “X-ray” image (as it came to be called) of his wife’s hand. Scientists around the world quickly began their own experiments with X-rays, and by 1900, X-rays were widely used to detect a variety of injuries and diseases. In 1901, Röntgen was awarded the first Nobel Prize for physics for his work in this field.

The **X-ray** is a form of high energy electromagnetic radiation with a short wavelength capable of penetrating solids and ionizing gases. As they are used in medicine, X-rays are emitted from an X-ray machine and directed toward a specially treated metallic plate placed behind the patient's body. The beam of radiation results in darkening of the X-ray plate. X-rays are slightly impeded by soft tissues, which show up as gray on the X-ray plate, whereas hard tissues, such as bone, largely block the rays, producing a light-toned "shadow." Thus, X-rays are best used to visualize hard body structures such as teeth and bones ([\[link\]](#)). Like many forms of high energy radiation, however, X-rays are capable of damaging cells and initiating changes that can lead to cancer. This danger of excessive exposure to X-rays was not fully appreciated for many years after their widespread use.

X-Ray of a Hand



High energy
electromagnetic radiation
allows the internal
structures of the body, such
as bones, to be seen in X-
rays like these. (credit:
Trace Meek/flickr)

Refinements and enhancements of X-ray techniques have continued throughout the twentieth and twenty-first centuries. Although often supplanted by more sophisticated imaging techniques, the X-ray remains a “workhorse” in medical imaging, especially for viewing fractures and for dentistry. The disadvantage of irradiation to the patient and the operator is now attenuated by proper shielding and by limiting exposure.

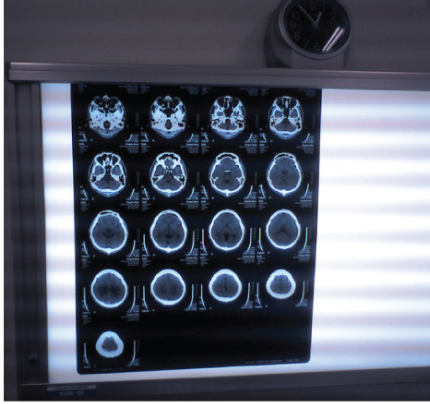
Modern Medical Imaging

X-rays can depict a two-dimensional image of a body region, and only from a single angle. In contrast, more recent medical imaging technologies produce data that is integrated and analyzed by computers to produce three-dimensional images or images that reveal aspects of body functioning.

Computed Tomography

Tomography refers to imaging by sections. **Computed tomography (CT)** is a noninvasive imaging technique that uses computers to analyze several cross-sectional X-rays in order to reveal minute details about structures in the body ([link](#)). The technique was invented in the 1970s and is based on the principle that, as X-rays pass through the body, they are absorbed or reflected at different levels. In the technique, a patient lies on a motorized platform while a computerized axial tomography (CAT) scanner rotates 360 degrees around the patient, taking X-ray images. A computer combines these images into a two-dimensional view of the scanned area, or “slice.”

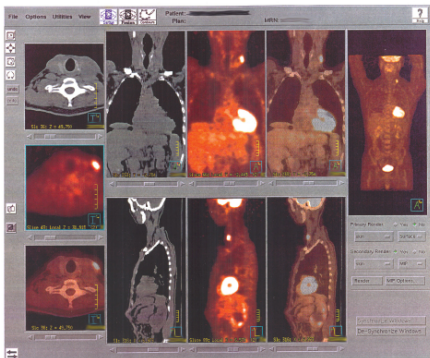
Medical Imaging Techniques



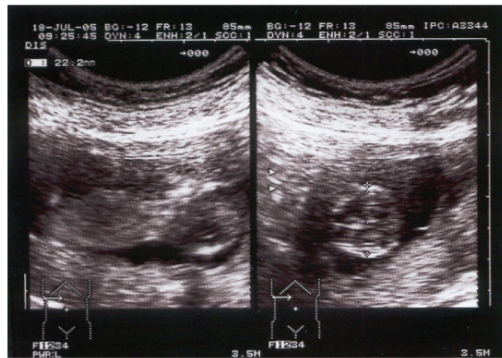
(a)



(b)



(c)



(d)

(a) The results of a CT scan of the head are shown as successive transverse sections. (b) An MRI machine generates a magnetic field around a patient. (c) PET scans use radiopharmaceuticals to create images of active blood flow and physiologic activity of the organ or organs being targeted. (d) Ultrasound technology is used to monitor pregnancies because it is the least invasive of imaging techniques and uses no electromagnetic radiation. (credit a: Akira Ohgaki/flickr; credit b: “Digital Cate”/flickr; credit c: “Raziel”/Wikimedia Commons; credit d: “Isis”/Wikimedia Commons)

Since 1970, the development of more powerful computers and more sophisticated software has made CT scanning routine for many types of

diagnostic evaluations. It is especially useful for soft tissue scanning, such as of the brain and the thoracic and abdominal viscera. Its level of detail is so precise that it can allow physicians to measure the size of a mass down to a millimeter. The main disadvantage of CT scanning is that it exposes patients to a dose of radiation many times higher than that of X-rays. In fact, children who undergo CT scans are at increased risk of developing cancer, as are adults who have multiple CT scans.

Note:



A CT or CAT scan relies on a circling scanner that revolves around the patient's body. Watch this [video](#) to learn more about CT and CAT scans. What type of radiation does a CT scanner use?

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a noninvasive medical imaging technique based on a phenomenon of nuclear physics discovered in the 1930s, in which matter exposed to magnetic fields and radio waves was found to emit radio signals. In 1970, a physician and researcher named Raymond Damadian noticed that malignant (cancerous) tissue gave off different signals than normal body tissue. He applied for a patent for the first MRI scanning device, which was in use clinically by the early 1980s. The early MRI scanners were crude, but advances in digital computing and electronics led to their advancement over any other technique for precise imaging, especially to discover tumors. MRI also has the major advantage of not exposing patients to radiation.

Drawbacks of MRI scans include their much higher cost, and patient discomfort with the procedure. The MRI scanner subjects the patient to such powerful electromagnets that the scan room must be shielded. The patient must be enclosed in a metal tube-like device for the duration of the scan (see [link](#)), sometimes as long as thirty minutes, which can be uncomfortable and impractical for ill patients. The device is also so noisy that, even with earplugs, patients can become anxious or even fearful. These problems have been overcome somewhat with the development of “open” MRI scanning, which does not require the patient to be entirely enclosed in the metal tube. Patients with iron-containing metallic implants (internal sutures, some prosthetic devices, and so on) cannot undergo MRI scanning because it can dislodge these implants.

Functional MRIs (fMRIs), which detect the concentration of blood flow in certain parts of the body, are increasingly being used to study the activity in parts of the brain during various body activities. This has helped scientists learn more about the locations of different brain functions and more about brain abnormalities and diseases.

Note:



A patient undergoing an MRI is surrounded by a tube-shaped scanner. Watch this [video](#) to learn more about MRIs. What is the function of magnets in an MRI?

Positron Emission Tomography

Positron emission tomography (PET) is a medical imaging technique involving the use of so-called radiopharmaceuticals, substances that emit radiation that is short-lived and therefore relatively safe to administer to the body. Although the first PET scanner was introduced in 1961, it took 15 more years before radiopharmaceuticals were combined with the technique and revolutionized its potential. The main advantage is that PET (see [\[link\]](#)c) can illustrate physiologic activity—including nutrient metabolism and blood flow—of the organ or organs being targeted, whereas CT and MRI scans can only show static images. PET is widely used to diagnose a multitude of conditions, such as heart disease, the spread of cancer, certain forms of infection, brain abnormalities, bone disease, and thyroid disease.

Note:



PET relies on radioactive substances administered several minutes before the scan. Watch this [video](#) to learn more about PET. How is PET used in chemotherapy?

Ultrasonography

Ultrasonography is an imaging technique that uses the transmission of high-frequency sound waves into the body to generate an echo signal that is converted by a computer into a real-time image of anatomy and physiology (see [\[link\]](#)d). Ultrasonography is the least invasive of all imaging techniques, and it is therefore used more freely in sensitive situations such as pregnancy. The technology was first developed in the 1940s and 1950s. Ultrasonography is used to study heart function, blood flow in the neck or extremities, certain conditions such as gallbladder disease, and fetal growth

and development. The main disadvantages of ultrasonography are that the image quality is heavily operator-dependent and that it is unable to penetrate bone and gas.

Chapter Review

Detailed anatomical drawings of the human body first became available in the fifteenth and sixteenth centuries; however, it was not until the end of the nineteenth century, and the discovery of X-rays, that anatomists and physicians discovered non-surgical methods to look inside a living body. Since then, many other techniques, including CT scans, MRI scans, PET scans, and ultrasonography, have been developed, providing more accurate and detailed views of the form and function of the human body.

Interactive Link Questions

Exercise:

Problem:

A CT or CAT scan relies on a circling scanner that revolves around the patient's body. Watch this [video](#) to learn more about CT and CAT scans. What type of radiation does a CT scanner use?

Solution:

X-rays.

Exercise:

Problem:

A patient undergoing an MRI is surrounded by a tube-shaped scanner. Watch this [video](#) to learn more about MRIs. What is the function of magnets in an MRI?

Solution:

The magnets induce tissue to emit radio signals that can show differences between different types of tissue.

Exercise:

Problem:

PET relies on radioactive substances administered several minutes before the scan. Watch this [video](#) to learn more about PET. How is PET used in chemotherapy?

Solution:

PET scans can indicate how patients are responding to chemotherapy.

Review Questions

Exercise:

Problem:

In 1901, Wilhelm Röntgen was the first person to win the Nobel Prize for physics. For what discovery did he win?

- a. nuclear physics
 - b. radiopharmaceuticals
 - c. the link between radiation and cancer
 - d. X-rays
-

Solution:

D

Exercise:

Problem:

Which of the following imaging techniques would be best to use to study the uptake of nutrients by rapidly multiplying cancer cells?

- a. CT
 - b. MRI
 - c. PET
 - d. ultrasonography
-

Solution:

C

Exercise:

Problem:

Which of the following imaging studies can be used most safely during pregnancy?

- a. CT scans
 - b. PET scans
 - c. ultrasounds
 - d. X-rays
-

Solution:

C

Exercise:

Problem: What are two major disadvantages of MRI scans?

- a. release of radiation and poor quality images
 - b. high cost and the need for shielding from the magnetic signals
 - c. can only view metabolically active tissues and inadequate availability of equipment
 - d. release of radiation and the need for a patient to be confined to metal tube for up to 30 minutes
-

Solution:

B

Critical Thinking Questions

Exercise:

Problem:

Which medical imaging technique is most dangerous to use repeatedly, and why?

Solution:

CT scanning subjects patients to much higher levels of radiation than X-rays, and should not be performed repeatedly.

Exercise:

Problem:

Explain why ultrasound imaging is the technique of choice for studying fetal growth and development.

Solution:

Ultrasonography does not expose a mother or fetus to radiation, to radiopharmaceuticals, or to magnetic fields. At this time, there are no known medical risks of ultrasonography.

Glossary

computed tomography (CT)

medical imaging technique in which a computer-enhanced cross-sectional X-ray image is obtained

magnetic resonance imaging (MRI)

medical imaging technique in which a device generates a magnetic field to obtain detailed sectional images of the internal structures of the

body

positron emission tomography (PET)

medical imaging technique in which radiopharmaceuticals are traced to reveal metabolic and physiological functions in tissues

ultrasonography

application of ultrasonic waves to visualize subcutaneous body structures such as tendons and organs

X-ray

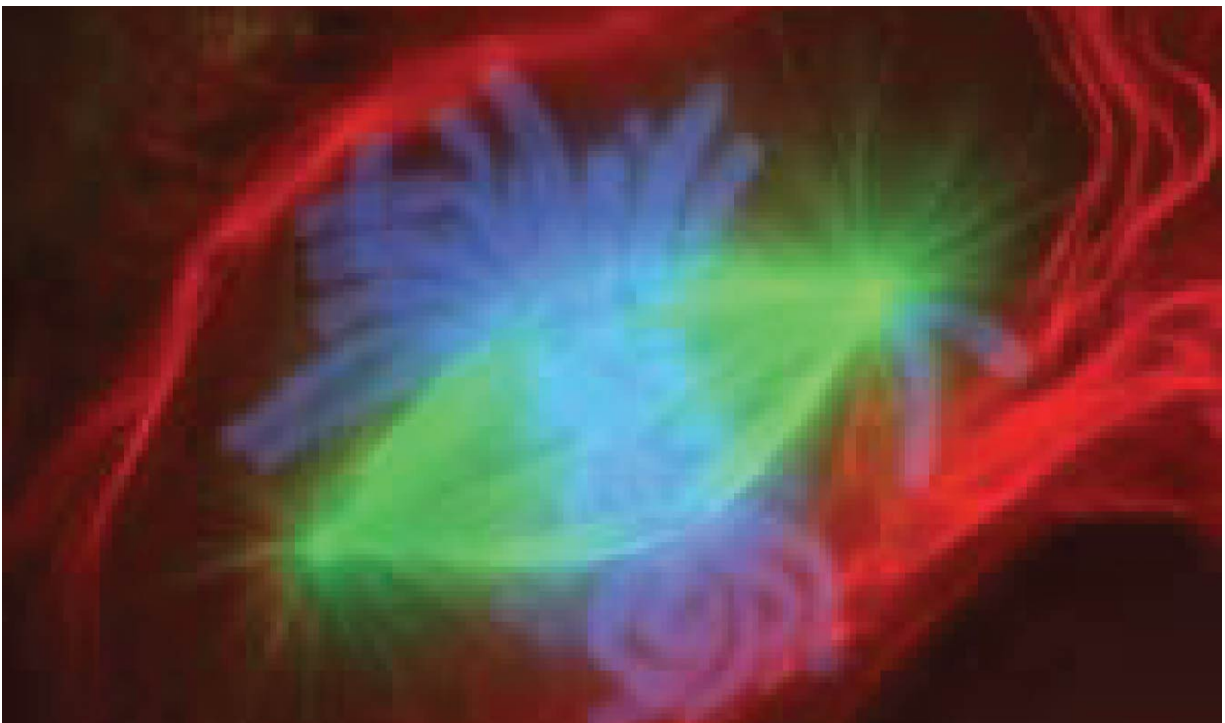
form of high energy electromagnetic radiation with a short wavelength capable of penetrating solids and ionizing gases; used in medicine as a diagnostic aid to visualize body structures such as bones

Introduction

class="introduction"

Fluorescence-stained Cell Undergoing Mitosis

A lung cell from a newt, commonly studied for its similarity to human lung cells, is stained with fluorescent dyes. The green stain reveals mitotic spindles, red is the cell membrane and part of the cytoplasm, and the structures that appear light blue are chromosomes. This cell is in anaphase of mitosis. (credit: "Mortadelo2005"/Wikimedia Commons)



Note:**Chapter Objectives**

After studying this chapter, you will be able to:

- Describe the structure and function of the cell membrane, including its regulation of materials into and out of the cell
- Describe the functions of the various cytoplasmic organelles
- Explain the structure and contents of the nucleus, as well as the process of DNA replication
- Explain the process by which a cell builds proteins using the DNA code
- List the stages of the cell cycle in order, including the steps of cell division in somatic cells
- Discuss how a cell differentiates and becomes more specialized
- List the morphological and physiological characteristics of some representative cell types in the human body

You developed from a single fertilized egg cell into the complex organism containing trillions of cells that you see when you look in a mirror. During this developmental process, early, undifferentiated cells differentiate and become specialized in their structure and function. These different cell types form specialized tissues that work in concert to perform all of the functions necessary for the living organism. Cellular and developmental biologists study how the continued division of a single cell leads to such complexity and differentiation.

Consider the difference between a structural cell in the skin and a nerve cell. A structural skin cell may be shaped like a flat plate (squamous) and live only for a short time before it is shed and replaced. Packed tightly into rows and sheets, the squamous skin cells provide a protective barrier for the cells and tissues that lie beneath. A nerve cell, on the other hand, may be shaped something like a star, sending out long processes up to a meter in length and may live for the entire lifetime of the organism. With their long winding appendages, nerve cells can communicate with one another and with other types of body cells and send rapid signals that inform the

organism about its environment and allow it to interact with that environment. These differences illustrate one very important theme that is consistent at all organizational levels of biology: the form of a structure is optimally suited to perform particular functions assigned to that structure. Keep this theme in mind as you tour the inside of a cell and are introduced to the various types of cells in the body.

A primary responsibility of each cell is to contribute to homeostasis. Homeostasis is a term used in biology that refers to a dynamic state of balance within parameters that are compatible with life. For example, living cells require a water-based environment to survive in, and there are various physical (anatomical) and physiological mechanisms that keep all of the trillions of living cells in the human body moist. This is one aspect of homeostasis. When a particular parameter, such as blood pressure or blood oxygen content, moves far enough *out* of homeostasis (generally becoming too high or too low), illness or disease—and sometimes death—inevitably results.

The concept of a cell started with microscopic observations of dead cork tissue by scientist Robert Hooke in 1665. Without realizing their function or importance, Hook coined the term “cell” based on the resemblance of the small subdivisions in the cork to the rooms that monks inhabited, called cells. About ten years later, Antonie van Leeuwenhoek became the first person to observe living and moving cells under a microscope. In the century that followed, the theory that cells represented the basic unit of life would develop. These tiny fluid-filled sacs house components responsible for the thousands of biochemical reactions necessary for an organism to grow and survive. In this chapter, you will learn about the major components and functions of a prototypical, generalized cell and discover some of the different types of cells in the human body.

The Cell Membrane

By the end of this section, you will be able to:

- Describe the molecular components that make up the cell membrane
- Explain the major features and properties of the cell membrane
- Differentiate between materials that can and cannot diffuse through the lipid bilayer
- Compare and contrast different types of passive transport with active transport, providing examples of each

Despite differences in structure and function, all living cells in multicellular organisms have a surrounding cell membrane. As the outer layer of your skin separates your body from its environment, the cell membrane (also known as the plasma membrane) separates the inner contents of a cell from its exterior environment. This cell membrane provides a protective barrier around the cell and regulates which materials can pass in or out.

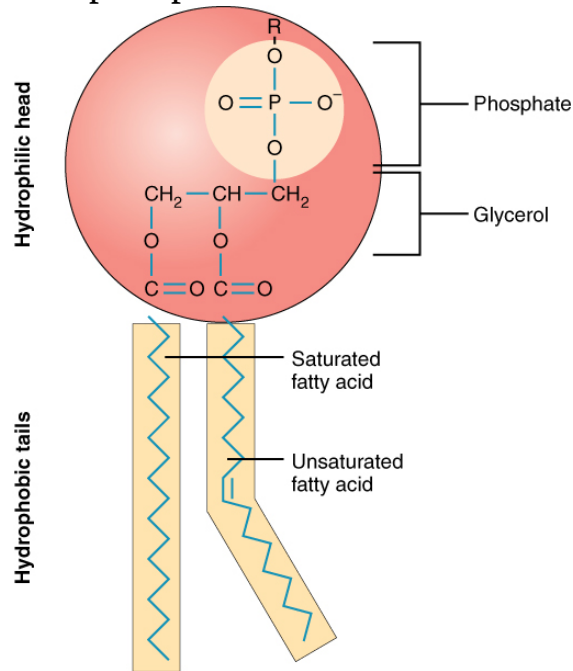
Structure and Composition of the Cell Membrane

The **cell membrane** is an extremely pliable structure composed primarily of back-to-back phospholipids (a “bilayer”). Cholesterol is also present, which contributes to the fluidity of the membrane, and there are various proteins embedded within the membrane that have a variety of functions.

A single phospholipid molecule has a phosphate group on one end, called the “head,” and two side-by-side chains of fatty acids that make up the lipid tails ([link](#)). The phosphate group is negatively charged, making the head polar and hydrophilic—or “water loving.” A **hydrophilic** molecule (or region of a molecule) is one that is attracted to water. The phosphate heads are thus attracted to the water molecules of both the extracellular and intracellular environments. The lipid tails, on the other hand, are uncharged, or nonpolar, and are hydrophobic—or “water fearing.” A **hydrophobic** molecule (or region of a molecule) repels and is repelled by water. Some lipid tails consist of saturated fatty acids and some contain unsaturated fatty acids. This combination adds to the fluidity of the tails that are constantly in motion. Phospholipids are thus amphipathic molecules. An **amphipathic** molecule is one that contains both a hydrophilic and a hydrophobic region.

In fact, soap works to remove oil and grease stains because it has amphipathic properties. The hydrophilic portion can dissolve in water while the hydrophobic portion can trap grease in micelles that then can be washed away.

Phospholipid Structure



A phospholipid molecule consists of a polar phosphate “head,” which is hydrophilic and a non-polar lipid “tail,” which is hydrophobic.

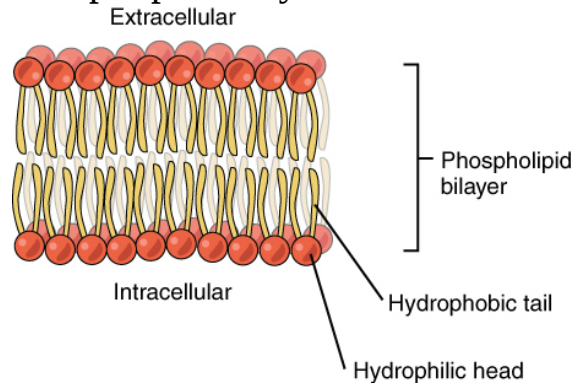
Unsaturated fatty acids result in kinks in the hydrophobic tails.

The cell membrane consists of two adjacent layers of phospholipids. The lipid tails of one layer face the lipid tails of the other layer, meeting at the interface of the two layers. The phospholipid heads face outward, one layer exposed to the interior of the cell and one layer exposed to the exterior ([link](#)). Because the phosphate groups are polar and hydrophilic, they are

attracted to water in the intracellular fluid. **Intracellular fluid (ICF)** is the fluid interior of the cell. The phosphate groups are also attracted to the extracellular fluid. **Extracellular fluid (ECF)** is the fluid environment outside the enclosure of the cell membrane. **Interstitial fluid (IF)** is the term given to extracellular fluid not contained within blood vessels.

Because the lipid tails are hydrophobic, they meet in the inner region of the membrane, excluding watery intracellular and extracellular fluid from this space. The cell membrane has many proteins, as well as other lipids (such as cholesterol), that are associated with the phospholipid bilayer. An important feature of the membrane is that it remains fluid; the lipids and proteins in the cell membrane are not rigidly locked in place.

Phospholipid Bilayer



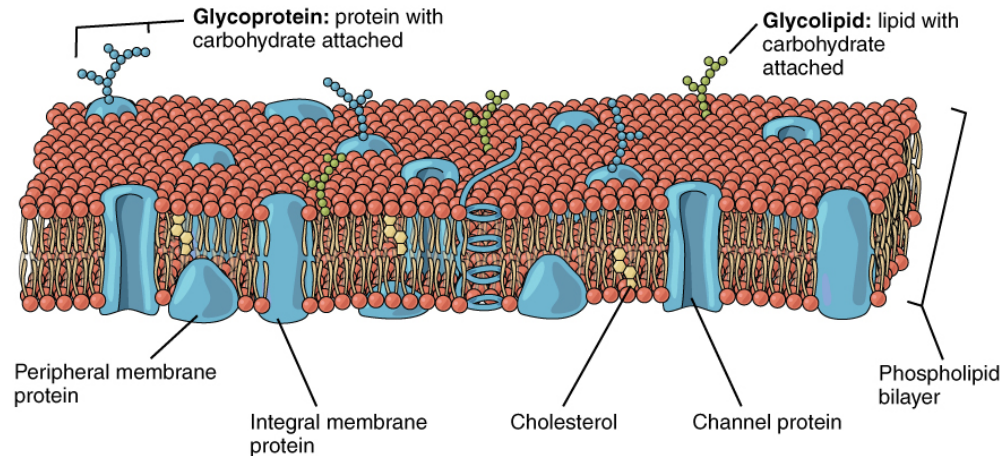
The phospholipid bilayer consists of two adjacent sheets of phospholipids, arranged tail to tail. The hydrophobic tails associate with one another, forming the interior of the membrane.

The polar heads contact the fluid inside and outside of the cell.

Membrane Proteins

The lipid bilayer forms the basis of the cell membrane, but it is peppered throughout with various proteins. Two different types of proteins that are commonly associated with the cell membrane are the integral proteins and peripheral protein ([\[link\]](#)). As its name suggests, an **integral protein** is a protein that is embedded in the membrane. A **channel protein** is an example of an integral protein that selectively allows particular materials, such as certain ions, to pass into or out of the cell.

Cell Membrane



The cell membrane of the cell is a phospholipid bilayer containing many different molecular components, including proteins and cholesterol, some with carbohydrate groups attached.

Another important group of integral proteins are cell recognition proteins, which serve to mark a cell's identity so that it can be recognized by other cells. A **receptor** is a type of recognition protein that can selectively bind a specific molecule outside the cell, and this binding induces a chemical reaction within the cell. A **ligand** is the specific molecule that binds to and activates a receptor. Some integral proteins serve dual roles as both a receptor and an ion channel. One example of a receptor-ligand interaction is the receptors on nerve cells that bind neurotransmitters, such as dopamine. When a dopamine molecule binds to a dopamine receptor protein, a channel within the transmembrane protein opens to allow certain ions to flow into the cell.

Some integral membrane proteins are glycoproteins. A **glycoprotein** is a protein that has carbohydrate molecules attached, which extend into the extracellular matrix. The attached carbohydrate tags on glycoproteins aid in cell recognition. The carbohydrates that extend from membrane proteins and even from some membrane lipids collectively form the glycocalyx. The **glycocalyx** is a fuzzy-appearing coating around the cell formed from glycoproteins and other carbohydrates attached to the cell membrane. The glycocalyx can have various roles. For example, it may have molecules that allow the cell to bind to another cell, it may contain receptors for hormones, or it might have enzymes to break down nutrients. The glycocalyxes found in a person's body are products of that person's genetic makeup. They give each of the individual's trillions of cells the "identity" of belonging in the person's body. This identity is the primary way that a person's immune defense cells "know" not to attack the person's own body cells, but it also is the reason organs donated by another person might be rejected.

Peripheral proteins are typically found on the inner or outer surface of the lipid bilayer but can also be attached to the internal or external surface of an integral protein. These proteins typically perform a specific function for the cell. Some peripheral proteins on the surface of intestinal cells, for example, act as digestive enzymes to break down nutrients to sizes that can pass through the cells and into the bloodstream.

Transport across the Cell Membrane

One of the great wonders of the cell membrane is its ability to regulate the concentration of substances inside the cell. These substances include ions such as Ca^{++} , Na^+ , K^+ , and Cl^- ; nutrients including sugars, fatty acids, and amino acids; and waste products, particularly carbon dioxide (CO_2), which must leave the cell.

The membrane's lipid bilayer structure provides the first level of control. The phospholipids are tightly packed together, and the membrane has a hydrophobic interior. This structure causes the membrane to be selectively permeable. A membrane that has **selective permeability** allows only substances meeting certain criteria to pass through it unaided. In the case of the cell membrane, only relatively small, nonpolar materials can move

through the lipid bilayer (remember, the lipid tails of the membrane are nonpolar). Some examples of these are other lipids, oxygen and carbon dioxide gases, and alcohol. However, water-soluble materials—like glucose, amino acids, and electrolytes—need some assistance to cross the membrane because they are repelled by the hydrophobic tails of the phospholipid bilayer. All substances that move through the membrane do so by one of two general methods, which are categorized based on whether or not energy is required. **Passive transport** is the movement of substances across the membrane without the expenditure of cellular energy. In contrast, **active transport** is the movement of substances across the membrane using energy from adenosine triphosphate (ATP).

Passive Transport

In order to understand *how* substances move passively across a cell membrane, it is necessary to understand concentration gradients and diffusion. A **concentration gradient** is the difference in concentration of a substance across a space. Molecules (or ions) will spread/diffuse from where they are more concentrated to where they are less concentrated until they are equally distributed in that space. (When molecules move in this way, they are said to move *down* their concentration gradient.) **Diffusion** is the movement of particles from an area of higher concentration to an area of lower concentration. A couple of common examples will help to illustrate this concept. Imagine being inside a closed bathroom. If a bottle of perfume were sprayed, the scent molecules would naturally diffuse from the spot where they left the bottle to all corners of the bathroom, and this diffusion would go on until no more concentration gradient remains. Another example is a spoonful of sugar placed in a cup of tea. Eventually the sugar will diffuse throughout the tea until no concentration gradient remains. In both cases, if the room is warmer or the tea hotter, diffusion occurs even faster as the molecules are bumping into each other and spreading out faster than at cooler temperatures. Having an internal body temperature around 98.6° F thus also aids in diffusion of particles within the body.

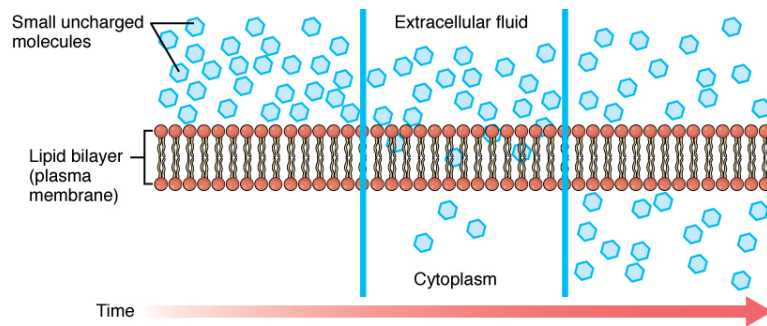
Note:

Visit this [link](#) to see diffusion and how it is propelled by the kinetic energy of molecules in solution. How does temperature affect diffusion rate, and why?

Whenever a substance exists in greater concentration on one side of a semipermeable membrane, such as the cell membranes, any substance that can move down its concentration gradient across the membrane will do so. Consider substances that can easily diffuse through the lipid bilayer of the cell membrane, such as the gases oxygen (O_2) and CO_2 . O_2 generally diffuses into cells because it is more concentrated outside of them, and CO_2 typically diffuses out of cells because it is more concentrated inside of them. Neither of these examples requires any energy on the part of the cell, and therefore they use passive transport to move across the membrane.

Before moving on, you need to review the gases that can diffuse across a cell membrane. Because cells rapidly use up oxygen during metabolism, there is typically a lower concentration of O_2 inside the cell than outside. As a result, oxygen will diffuse from the interstitial fluid directly through the lipid bilayer of the membrane and into the cytoplasm within the cell. On the other hand, because cells produce CO_2 as a byproduct of metabolism, CO_2 concentrations rise within the cytoplasm; therefore, CO_2 will move from the cell through the lipid bilayer and into the interstitial fluid, where its concentration is lower. This mechanism of molecules moving across a cell membrane from the side where they are more concentrated to the side where they are less concentrated is a form of passive transport called simple diffusion ([link](#)).

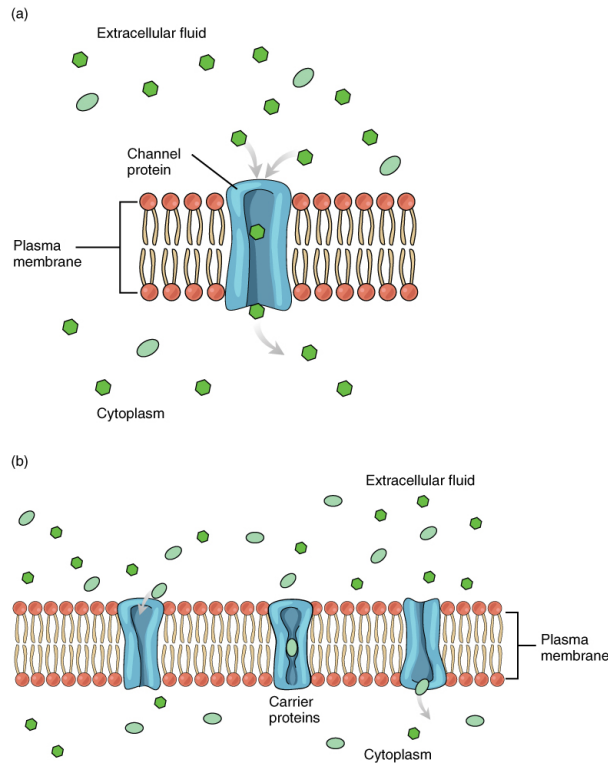
Simple Diffusion across the Cell (Plasma) Membrane



The structure of the lipid bilayer allows small, uncharged substances such as oxygen and carbon dioxide, and hydrophobic molecules such as lipids, to pass through the cell membrane, down their concentration gradient, by simple diffusion.

Large polar or ionic molecules, which are hydrophilic, cannot easily cross the phospholipid bilayer. Very small polar molecules, such as water, can cross via simple diffusion due to their small size. Charged atoms or molecules of any size cannot cross the cell membrane via simple diffusion as the charges are repelled by the hydrophobic tails in the interior of the phospholipid bilayer. Solutes dissolved in water on either side of the cell membrane will tend to diffuse down their concentration gradients, but because most substances cannot pass freely through the lipid bilayer of the cell membrane, their movement is restricted to protein channels and specialized transport mechanisms in the membrane. **Facilitated diffusion** is the diffusion process used for those substances that cannot cross the lipid bilayer due to their size, charge, and/or polarity ([\[link\]](#)). A common example of facilitated diffusion is the movement of glucose into the cell, where it is used to make ATP. Although glucose can be more concentrated outside of a cell, it cannot cross the lipid bilayer via simple diffusion because it is both large and polar. To resolve this, a specialized carrier protein called the glucose transporter will transfer glucose molecules into the cell to facilitate its inward diffusion.

Facilitated Diffusion



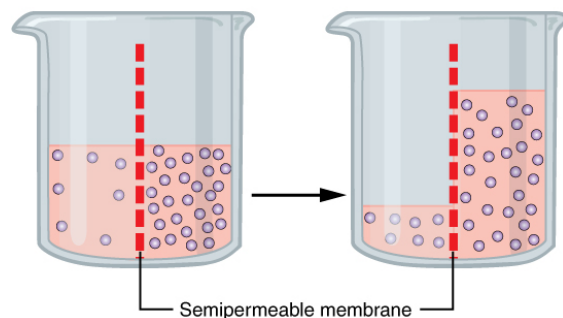
- (a) Facilitated diffusion of substances crossing the cell (plasma) membrane takes place with the help of proteins such as channel proteins and carrier proteins. Channel proteins are less selective than carrier proteins, and usually mildly discriminate between their cargo based on size and charge.
- (b) Carrier proteins are more selective, often only allowing one particular type of molecule to cross.

As an example, even though sodium ions (Na^+) are highly concentrated outside of cells, these electrolytes are charged and cannot pass through the

nonpolar lipid bilayer of the membrane. Their diffusion is facilitated by membrane proteins that form sodium channels (or “pores”), so that Na^+ ions can move down their concentration gradient from outside the cells to inside the cells. There are many other solutes that must undergo facilitated diffusion to move into a cell, such as amino acids, or to move out of a cell, such as wastes. Because facilitated diffusion is a passive process, it does not require energy expenditure by the cell.

Water also can move freely across the cell membrane of all cells, either through protein channels or by slipping between the lipid tails of the membrane itself. **Osmosis** is the diffusion of water through a semipermeable membrane ([\[link\]](#)).

Osmosis

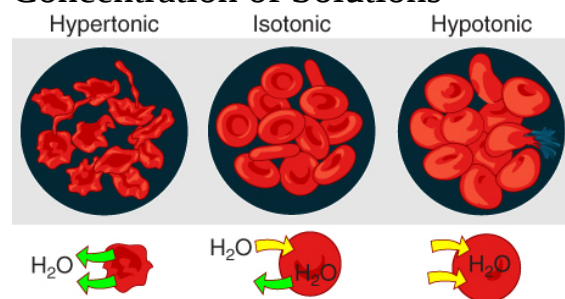


Osmosis is the diffusion of water through a semipermeable membrane down its concentration gradient. If a membrane is permeable to water, though not to a solute, water will equalize its own concentration by diffusing to the side of lower water concentration (and thus the side of higher solute concentration). In the beaker on the left, the solution on the right side of the membrane is hypertonic.

The movement of water molecules is not itself regulated by cells, so it is important that cells are exposed to an environment in which the concentration of solutes outside of the cells (in the extracellular fluid) is equal to the concentration of solutes inside the cells (in the cytoplasm). Two solutions that have the same concentration of solutes are said to be **isotonic** (equal tension). When cells and their extracellular environments are isotonic, the concentration of water molecules is the same outside and inside the cells, and the cells maintain their normal shape (and function).

Osmosis occurs when there is an imbalance of solutes outside of a cell versus inside the cell. A solution that has a higher concentration of solutes than another solution is said to be **hypertonic**, and water molecules tend to diffuse into a hypertonic solution ([\[link\]](#)). Cells in a hypertonic solution will shrivel as water leaves the cell via osmosis. In contrast, a solution that has a lower concentration of solutes than another solution is said to be **hypotonic**, and water molecules tend to diffuse out of a hypotonic solution. Cells in a hypotonic solution will take on too much water and swell, with the risk of eventually bursting. A critical aspect of homeostasis in living things is to create an internal environment in which all of the body's cells are in an isotonic solution. Various organ systems, particularly the kidneys, work to maintain this homeostasis.

Concentration of Solutions



A hypertonic solution has a solute concentration higher than another solution. An isotonic solution has a solute concentration equal to

another solution. A hypotonic solution has a solute concentration lower than another solution.

Another mechanism besides diffusion to passively transport materials between compartments is filtration. Unlike diffusion of a substance from where it is more concentrated to less concentrated, filtration uses a hydrostatic pressure gradient that pushes the fluid—and the solutes within it—from a higher pressure area to a lower pressure area. Filtration is an extremely important process in the body. For example, the circulatory system uses filtration to move plasma and substances across the endothelial lining of capillaries and into surrounding tissues, supplying cells with the nutrients. Filtration pressure in the kidneys provides the mechanism to remove wastes from the bloodstream.

Active Transport

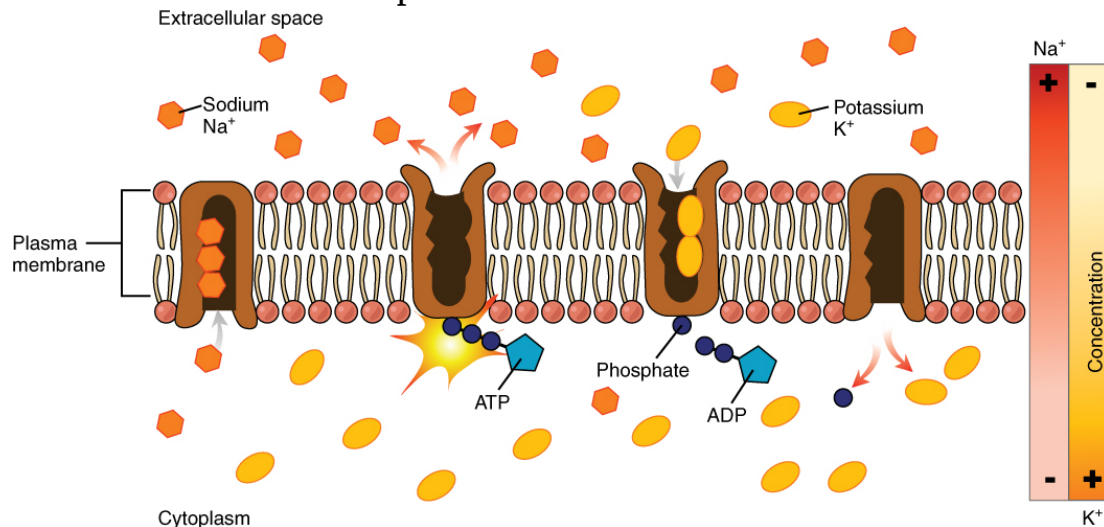
For all of the transport methods described above, the cell expends no energy. Membrane proteins that aid in the passive transport of substances do so without the use of ATP. During active transport, ATP is required to move a substance across a membrane, often with the help of protein carriers, and usually *against* its concentration gradient.

One of the most common types of active transport involves proteins that serve as pumps. The word “pump” probably conjures up thoughts of using energy to pump up the tire of a bicycle or a basketball. Similarly, energy from ATP is required for these membrane proteins to transport substances—molecules or ions—across the membrane, usually against their concentration gradients (from an area of low concentration to an area of high concentration).

The **sodium-potassium pump**, which is also called Na^+/K^+ ATPase, transports sodium out of a cell while moving potassium into the cell. The

Na^+/K^+ pump is an important ion pump found in the membranes of many types of cells. These pumps are particularly abundant in nerve cells, which are constantly pumping out sodium ions and pulling in potassium ions to maintain an electrical gradient across their cell membranes. An **electrical gradient** is a difference in electrical charge across a space. In the case of nerve cells, for example, the electrical gradient exists between the inside and outside of the cell, with the inside being negatively-charged (at around -70 mV) relative to the outside. The negative electrical gradient is maintained because each Na^+/K^+ pump moves three Na^+ ions out of the cell and two K^+ ions into the cell for each ATP molecule that is used ([\[link\]](#)). This process is so important for nerve cells that it accounts for the majority of their ATP usage.

Sodium-Potassium Pump



The sodium-potassium pump is found in many cell (plasma) membranes. Powered by ATP, the pump moves sodium and potassium ions in opposite directions, each against its concentration gradient. In a single cycle of the pump, three sodium ions are extruded from and two potassium ions are imported into the cell.

Active transport pumps can also work together with other active or passive transport systems to move substances across the membrane. For example, the sodium-potassium pump maintains a high concentration of sodium ions

outside of the cell. Therefore, if the cell needs sodium ions, all it has to do is open a passive sodium channel, as the concentration gradient of the sodium ions will drive them to diffuse into the cell. In this way, the action of an active transport pump (the sodium-potassium pump) powers the passive transport of sodium ions by creating a concentration gradient. When active transport powers the transport of another substance in this way, it is called secondary active transport.

Symporters are secondary active transporters that move two substances in the same direction. For example, the sodium-glucose symporter uses sodium ions to “pull” glucose molecules into the cell. Because cells store glucose for energy, glucose is typically at a higher concentration inside of the cell than outside. However, due to the action of the sodium-potassium pump, sodium ions will easily diffuse into the cell when the symporter is opened. The flood of sodium ions through the symporter provides the energy that allows glucose to move through the symporter and into the cell, against its concentration gradient.

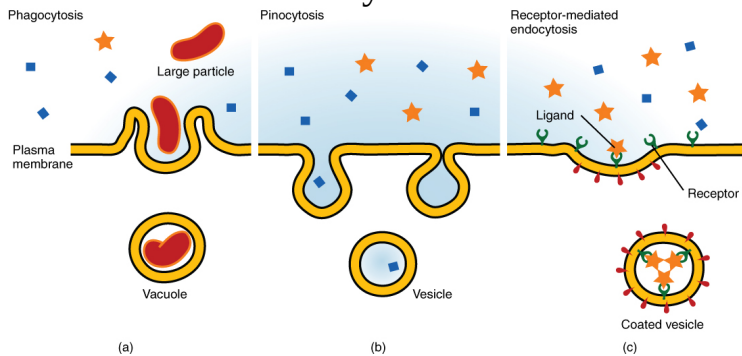
Conversely, antiporters are secondary active transport systems that transport substances in opposite directions. For example, the sodium-hydrogen ion antiporter uses the energy from the inward flood of sodium ions to move hydrogen ions (H^+) out of the cell. The sodium-hydrogen antiporter is used to maintain the pH of the cell's interior.

Other forms of active transport do not involve membrane carriers.

Endocytosis (bringing “into the cell”) is the process of a cell ingesting material by enveloping it in a portion of its cell membrane, and then pinching off that portion of membrane ([link](#)). Once pinched off, the portion of membrane and its contents becomes an independent, intracellular vesicle. A **vesicle** is a membranous sac—a spherical and hollow organelle bounded by a lipid bilayer membrane. Endocytosis often brings materials into the cell that must to be broken down or digested. **Phagocytosis** (“cell eating”) is the endocytosis of large particles. Many immune cells engage in phagocytosis of invading pathogens. Like little Pac-men, their job is to patrol body tissues for unwanted matter, such as invading bacterial cells, phagocytize them, and digest them. In contrast to phagocytosis, **pinocytosis**

(“cell drinking”) brings fluid containing dissolved substances into a cell through membrane vesicles.

Three Forms of Endocytosis



Endocytosis is a form of active transport in which a cell envelopes extracellular materials using its cell membrane. (a) In phagocytosis, which is relatively nonselective, the cell takes in a large particle. (b) In pinocytosis, the cell takes in small particles in fluid. (c) In contrast, receptor-mediated endocytosis is quite selective. When external receptors bind a specific ligand, the cell responds by endocytosing the ligand.

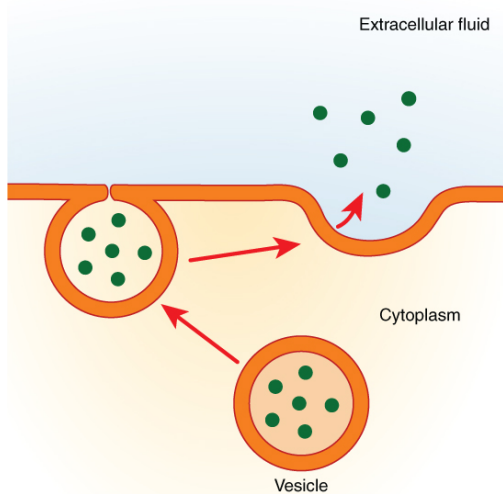
Phagocytosis and pinocytosis take in large portions of extracellular material, and they are typically not highly selective in the substances they bring in. Cells regulate the endocytosis of specific substances via receptor-mediated endocytosis. **Receptor-mediated endocytosis** is endocytosis by a portion of the cell membrane that contains many receptors that are specific for a certain substance. Once the surface receptors have bound sufficient amounts of the specific substance (the receptor’s ligand), the cell will endocytose the part of the cell membrane containing the receptor-ligand complexes. Iron, a required component of hemoglobin, is endocytosed by red blood cells in this way. Iron is bound to a protein called transferrin in the blood. Specific transferrin receptors on red blood cell surfaces bind the

iron-transferrin molecules, and the cell endocytoses the receptor-ligand complexes.

In contrast with endocytosis, **exocytosis** (taking “out of the cell”) is the process of a cell exporting material using vesicular transport ([\[link\]](#)). Many cells manufacture substances that must be secreted, like a factory manufacturing a product for export. These substances are typically packaged into membrane-bound vesicles within the cell. When the vesicle membrane fuses with the cell membrane, the vesicle releases its contents into the interstitial fluid. The vesicle membrane then becomes part of the cell membrane. Cells of the stomach and pancreas produce and secrete digestive enzymes through exocytosis ([\[link\]](#)). Endocrine cells produce and secrete hormones that are sent throughout the body, and certain immune cells produce and secrete large amounts of histamine, a chemical important for immune responses.

Exocytosis

Exocytosis



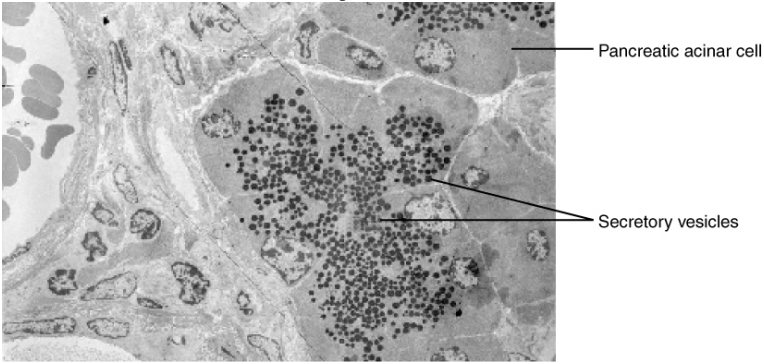
Exocytosis is much like endocytosis in reverse.

Material destined for export is packaged into a vesicle inside the cell.

The membrane of the vesicle fuses with the cell membrane, and the

contents are released into
the extracellular space.

Pancreatic Cells' Enzyme Products



The pancreatic acinar cells produce and secrete many enzymes that digest food. The tiny black granules in this electron micrograph are secretory vesicles filled with enzymes that will be exported from the cells via exocytosis. LM $\times 2900$.

(Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:



View the [University of Michigan WebScope](#) to explore the tissue sample in greater detail.

Note:

Diseases of the...

Cell: Cystic Fibrosis

Cystic fibrosis (CF) affects approximately 30,000 people in the United States, with about 1,000 new cases reported each year. The genetic disease is most well known for its damage to the lungs, causing breathing difficulties and chronic lung infections, but it also affects the liver, pancreas, and intestines. Only about 50 years ago, the prognosis for children born with CF was very grim—a life expectancy rarely over 10 years. Today, with advances in medical treatment, many CF patients live into their 30s.

The symptoms of CF result from a malfunctioning membrane ion channel called the cystic fibrosis transmembrane conductance regulator, or CFTR. In healthy people, the CFTR protein is an integral membrane protein that transports Cl^- ions out of the cell. In a person who has CF, the gene for the CFTR is mutated, thus, the cell manufactures a defective channel protein that typically is not incorporated into the membrane, but is instead degraded by the cell.

The CFTR requires ATP in order to function, making its Cl^- transport a form of active transport. This characteristic puzzled researchers for a long time because the Cl^- ions are actually flowing *down* their concentration gradient when transported out of cells. Active transport generally pumps ions *against* their concentration gradient, but the CFTR presents an exception to this rule.

In normal lung tissue, the movement of Cl^- out of the cell maintains a Cl^- -rich, negatively charged environment immediately outside of the cell. This is particularly important in the epithelial lining of the respiratory system. Respiratory epithelial cells secrete mucus, which serves to trap dust, bacteria, and other debris. A cilium (plural = cilia) is one of the hair-like appendages found on certain cells. Cilia on the epithelial cells move the mucus and its trapped particles up the airways away from the lungs and toward the outside. In order to be effectively moved upward, the mucus

cannot be too viscous; rather it must have a thin, watery consistency. The transport of Cl^- and the maintenance of an electronegative environment outside of the cell attract positive ions such as Na^+ to the extracellular space. The accumulation of both Cl^- and Na^+ ions in the extracellular space creates solute-rich mucus, which has a low concentration of water molecules. As a result, through osmosis, water moves from cells and extracellular matrix into the mucus, “thinning” it out. This is how, in a normal respiratory system, the mucus is kept sufficiently watered-down to be propelled out of the respiratory system.

If the CFTR channel is absent, Cl^- ions are not transported out of the cell in adequate numbers, thus preventing them from drawing positive ions. The absence of ions in the secreted mucus results in the lack of a normal water concentration gradient. Thus, there is no osmotic pressure pulling water into the mucus. The resulting mucus is thick and sticky, and the ciliated epithelia cannot effectively remove it from the respiratory system. Passageways in the lungs become blocked with mucus, along with the debris it carries. Bacterial infections occur more easily because bacterial cells are not effectively carried away from the lungs.

Chapter Review

The cell membrane provides a barrier around the cell, separating its internal components from the extracellular environment. It is composed of a phospholipid bilayer, with hydrophobic internal lipid “tails” and hydrophilic external phosphate “heads.” Various membrane proteins are scattered throughout the bilayer, both inserted within it and attached to it peripherally. The cell membrane is selectively permeable, allowing only a limited number of materials to diffuse through its lipid bilayer. All materials that cross the membrane do so using passive (non energy-requiring) or active (energy-requiring) transport processes. During passive transport, materials move by simple diffusion or by facilitated diffusion through the membrane, down their concentration gradient. Water passes through the membrane in a diffusion process called osmosis. During active transport, energy is expended to assist material movement across the membrane in a

direction against their concentration gradient. Active transport may take place with the help of protein pumps or through the use of vesicles.

Interactive Link Questions

Exercise:

Problem:

Visit this [link](#) to see diffusion and how it is propelled by the kinetic energy of molecules in solution. How does temperature affect diffusion rate, and why?

Solution:

Higher temperatures speed up diffusion because molecules have more kinetic energy at higher temperatures.

Review Questions

Exercise:

Problem:

Because they are embedded within the membrane, ion channels are examples of _____.

- a. receptor proteins
 - b. integral proteins
 - c. peripheral proteins
 - d. glycoproteins
-

Solution:

B

Exercise:

Problem:

The diffusion of substances within a solution tends to move those substances _____ their _____ gradient.

- a. up; electrical
- b. up; electrochemical
- c. down; pressure
- d. down; concentration

Solution:

D

Exercise:

Problem: Ion pumps and phagocytosis are both examples of _____.

- a. endocytosis
- b. passive transport
- c. active transport
- d. facilitated diffusion

Solution:

C

Exercise:

Problem:

Choose the answer that best completes the following analogy:
Diffusion is to _____ as endocytosis is to _____.

- a. filtration; phagocytosis
- b. osmosis; pinocytosis
- c. solutes; fluid

d. gradient; chemical energy

Solution:

B

Critical Thinking Questions

Exercise:

Problem:

What materials can easily diffuse through the lipid bilayer, and why?

Solution:

Only materials that are relatively small and nonpolar can easily diffuse through the lipid bilayer. Large particles cannot fit in between the individual phospholipids that are packed together, and polar molecules are repelled by the hydrophobic/nonpolar lipids that line the inside of the bilayer.

Exercise:

Problem:

Why is receptor-mediated endocytosis said to be more selective than phagocytosis or pinocytosis?

Solution:

Receptor-mediated endocytosis is more selective because the substances that are brought into the cell are the specific ligands that could bind to the receptors being endocytosed. Phagocytosis or pinocytosis, on the other hand, have no such receptor-ligand specificity, and bring in whatever materials happen to be close to the membrane when it is enveloped.

Exercise:**Problem:**

What do osmosis, diffusion, filtration, and the movement of ions away from like charge all have in common? In what way do they differ?

Solution:

These four phenomena are similar in the sense that they describe the movement of substances down a particular type of gradient. Osmosis and diffusion involve the movement of water and other substances down their concentration gradients, respectively. Filtration describes the movement of particles down a pressure gradient, and the movement of ions away from like charge describes their movement down their electrical gradient.

Glossary

active transport

form of transport across the cell membrane that requires input of cellular energy

amphipathic

describes a molecule that exhibits a difference in polarity between its two ends, resulting in a difference in water solubility

cell membrane

membrane surrounding all animal cells, composed of a lipid bilayer interspersed with various molecules; also known as plasma membrane

channel protein

membrane-spanning protein that has an inner pore which allows the passage of one or more substances

concentration gradient

difference in the concentration of a substance between two regions

diffusion

movement of a substance from an area of higher concentration to one of lower concentration

electrical gradient

difference in the electrical charge (potential) between two regions

endocytosis

import of material into the cell by formation of a membrane-bound vesicle

exocytosis

export of a substance out of a cell by formation of a membrane-bound vesicle

extracellular fluid (ECF)

fluid exterior to cells; includes the interstitial fluid, blood plasma, and fluid found in other reservoirs in the body

facilitated diffusion

diffusion of a substance with the aid of a membrane protein

glycocalyx

coating of sugar molecules that surrounds the cell membrane

glycoprotein

protein that has one or more carbohydrates attached

hydrophilic

describes a substance or structure attracted to water

hydrophobic

describes a substance or structure repelled by water

hypertonic

describes a solution concentration that is higher than a reference concentration

hypotonic

describes a solution concentration that is lower than a reference concentration

integral protein

membrane-associated protein that spans the entire width of the lipid bilayer

interstitial fluid (IF)

fluid in the small spaces between cells not contained within blood vessels

intracellular fluid (ICF)

fluid in the cytosol of cells

isotonic

describes a solution concentration that is the same as a reference concentration

ligand

molecule that binds with specificity to a specific receptor molecule

osmosis

diffusion of water molecules down their concentration gradient across a selectively permeable membrane

passive transport

form of transport across the cell membrane that does not require input of cellular energy

peripheral protein

membrane-associated protein that does not span the width of the lipid bilayer, but is attached peripherally to integral proteins, membrane lipids, or other components of the membrane

phagocytosis

endocytosis of large particles

pinocytosis

endocytosis of fluid

receptor

protein molecule that contains a binding site for another specific molecule (called a ligand)

receptor-mediated endocytosis

endocytosis of ligands attached to membrane-bound receptors

selective permeability

feature of any barrier that allows certain substances to cross but excludes others

sodium-potassium pump

(also, Na^+/K^+ ATP-ase) membrane-embedded protein pump that uses ATP to move Na^+ out of a cell and K^+ into the cell

vesicle

membrane-bound structure that contains materials within or outside of the cell

Introduction
class="introduction"
Eating Apples

Eating may be one
of the simple
pleasures in life, but
digesting even one
apple requires the
coordinated work of
many organs. (credit:
“Aimanness
Photography”/Flickr
)



Note:**Chapter Objectives**

After studying this chapter, you will be able to:

- List and describe the functional anatomy of the organs and accessory organs of the digestive system
- Discuss the processes and control of ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation
- Discuss the roles of the liver, pancreas, and gallbladder in digestion
- Compare and contrast the digestion of the three macronutrients

The digestive system is continually at work, yet people seldom appreciate the complex tasks it performs in a choreographed biologic symphony. Consider what happens when you eat an apple. Of course, you enjoy the apple's taste as you chew it, but in the hours that follow, unless something goes amiss and you get a stomachache, you don't notice that your digestive system is working. You may be taking a walk or studying or sleeping, having forgotten all about the apple, but your stomach and intestines are busy digesting it and absorbing its vitamins and other nutrients. By the time any waste material is excreted, the body has appropriated all it can use from the apple. In short, whether you pay attention or not, the organs of the digestive system perform their specific functions, allowing you to use the food you eat to keep you going. This chapter examines the structure and functions of these organs, and explores the mechanics and chemistry of the digestive processes.

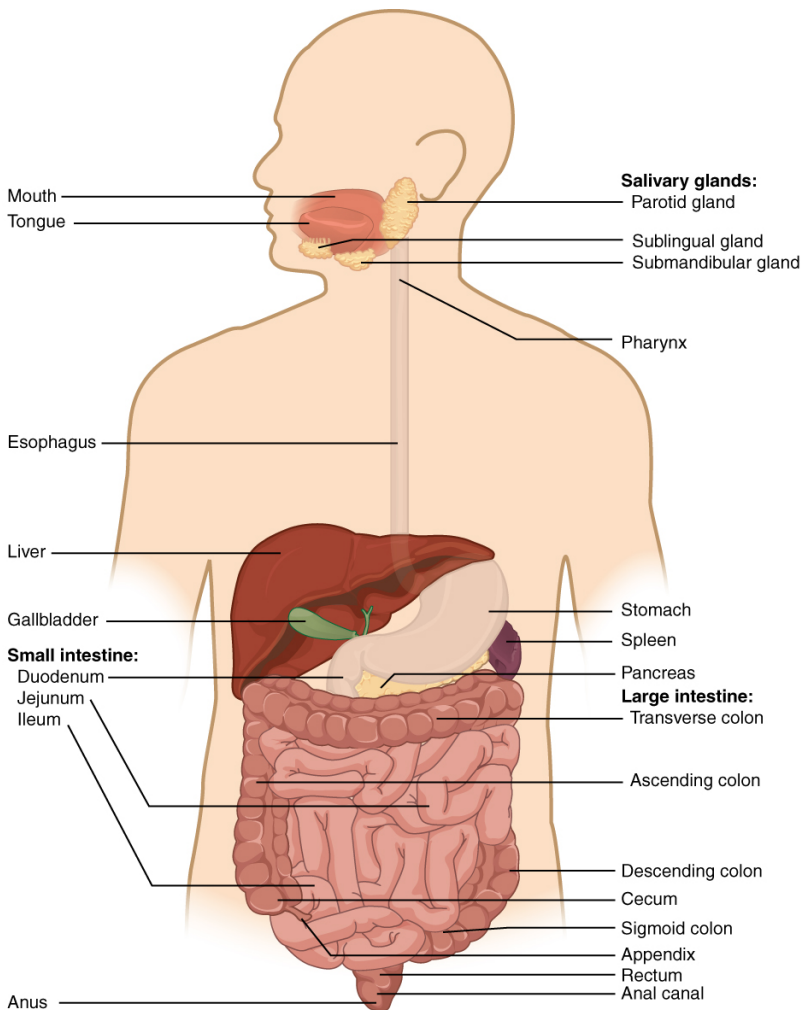
Overview of the Digestive System

By the end of this section, you will be able to:

- Identify the organs of the alimentary canal from proximal to distal, and briefly state their function
- Identify the accessory digestive organs and briefly state their function
- Describe the four fundamental tissue layers of the alimentary canal
- Contrast the contributions of the enteric and autonomic nervous systems to digestive system functioning
- Explain how the peritoneum anchors the digestive organs

The function of the digestive system is to break down the foods you eat, release their nutrients, and absorb those nutrients into the body. Although the small intestine is the workhorse of the system, where the majority of digestion occurs, and where most of the released nutrients are absorbed into the blood or lymph, each of the digestive system organs makes a vital contribution to this process ([\[link\]](#)).

Components of the Digestive System



All digestive organs play integral roles in the life-sustaining process of digestion.

As is the case with all body systems, the digestive system does not work in isolation; it functions cooperatively with the other systems of the body. Consider for example, the interrelationship between the digestive and cardiovascular systems. Arteries supply the digestive organs with oxygen and processed nutrients, and veins drain the digestive tract. These intestinal veins, constituting the hepatic portal system, are unique; they do not return blood directly to the heart. Rather, this blood is diverted to the liver where its nutrients are off-loaded for processing before blood completes its circuit back to the heart. At the same time, the digestive system provides nutrients

to the heart muscle and vascular tissue to support their functioning. The interrelationship of the digestive and endocrine systems is also critical. Hormones secreted by several endocrine glands, as well as endocrine cells of the pancreas, the stomach, and the small intestine, contribute to the control of digestion and nutrient metabolism. In turn, the digestive system provides the nutrients to fuel endocrine function. [\[link\]](#) gives a quick glimpse at how these other systems contribute to the functioning of the digestive system.

| Contribution of Other Body Systems to the Digestive System | |
|--|---|
| Body system | Benefits received by the digestive system |
| Cardiovascular | Blood supplies digestive organs with oxygen and processed nutrients |
| Endocrine | Endocrine hormones help regulate secretion in digestive glands and accessory organs |
| Integumentary | Skin helps protect digestive organs and synthesizes vitamin D for calcium absorption |
| Lymphatic | Mucosa-associated lymphoid tissue and other lymphatic tissue defend against entry of pathogens; lacteals absorb lipids; and lymphatic vessels transport lipids to bloodstream |
| Muscular | Skeletal muscles support and protect abdominal organs |

| Contribution of Other Body Systems to the Digestive System | |
|---|--|
| Body system | Benefits received by the digestive system |
| Nervous | Sensory and motor neurons help regulate secretions and muscle contractions in the digestive tract |
| Respiratory | Respiratory organs provide oxygen and remove carbon dioxide |
| Skeletal | Bones help protect and support digestive organs |
| Urinary | Kidneys convert vitamin D into its active form, allowing calcium absorption in the small intestine |

Digestive System Organs

The easiest way to understand the digestive system is to divide its organs into two main categories. The first group is the organs that make up the alimentary canal. Accessory digestive organs comprise the second group and are critical for orchestrating the breakdown of food and the assimilation of its nutrients into the body. Accessory digestive organs, despite their name, are critical to the function of the digestive system.

Alimentary Canal Organs

Also called the gastrointestinal (GI) tract or gut, the **alimentary canal** (aliment- = “to nourish”) is a one-way tube about 7.62 meters (25 feet) in length during life and closer to 10.67 meters (35 feet) in length when measured after death, once smooth muscle tone is lost. The main function of the organs of the alimentary canal is to nourish the body. This tube begins at the mouth and terminates at the anus. Between those two points, the canal is modified as the pharynx, esophagus, stomach, and small and

large intestines to fit the functional needs of the body. Both the mouth and anus are open to the external environment; thus, food and wastes within the alimentary canal are technically considered to be outside the body. Only through the process of absorption do the nutrients in food enter into and nourish the body's "inner space."

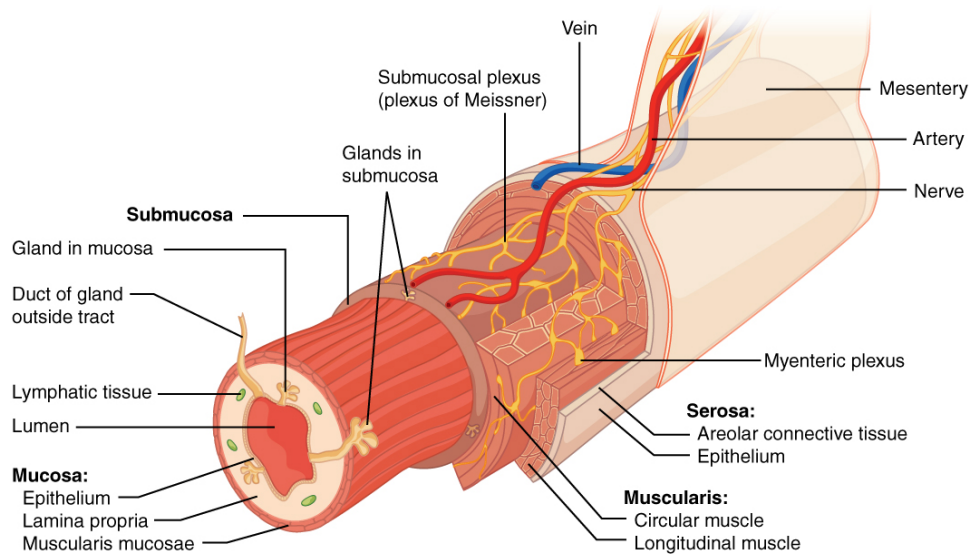
Accessory Structures

Each **accessory digestive organ** aids in the breakdown of food ([\[link\]](#)). Within the mouth, the teeth and tongue begin mechanical digestion, whereas the salivary glands begin chemical digestion. Once food products enter the small intestine, the gallbladder, liver, and pancreas release secretions—such as bile and enzymes—essential for digestion to continue. Together, these are called accessory organs because they sprout from the lining cells of the developing gut (mucosa) and augment its function; indeed, you could not live without their vital contributions, and many significant diseases result from their malfunction. Even after development is complete, they maintain a connection to the gut by way of ducts.

Histology of the Alimentary Canal

Throughout its length, the alimentary tract is composed of the same four tissue layers; the details of their structural arrangements vary to fit their specific functions. Starting from the lumen and moving outwards, these layers are the mucosa, submucosa, muscularis, and serosa, which is continuous with the mesentery (see [\[link\]](#)).

Layers of the Alimentary Canal



The wall of the alimentary canal has four basic tissue layers: the mucosa, submucosa, muscularis, and serosa.

The **mucosa** is referred to as a mucous membrane, because mucus production is a characteristic feature of gut epithelium. The membrane consists of epithelium, which is in direct contact with ingested food, and the lamina propria, a layer of connective tissue analogous to the dermis. In addition, the mucosa has a thin, smooth muscle layer, called the muscularis mucosa (not to be confused with the muscularis layer, described below).

Epithelium—In the mouth, pharynx, esophagus, and anal canal, the epithelium is primarily a non-keratinized, stratified squamous epithelium. In the stomach and intestines, it is a simple columnar epithelium. Notice that the epithelium is in direct contact with the lumen, the space inside the alimentary canal. Interspersed among its epithelial cells are goblet cells, which secrete mucus and fluid into the lumen, and enteroendocrine cells, which secrete hormones into the interstitial spaces between cells. Epithelial cells have a very brief lifespan, averaging from only a couple of days (in the mouth) to about a week (in the gut). This process of rapid renewal helps preserve the health of the alimentary canal, despite the wear and tear resulting from continued contact with foodstuffs.

Lamina propria—In addition to loose connective tissue, the lamina propria contains numerous blood and lymphatic vessels that transport nutrients absorbed through the alimentary canal to other parts of the body. The lamina propria also serves an immune function by housing clusters of lymphocytes, making up the mucosa-associated lymphoid tissue (MALT). These lymphocyte clusters are particularly substantial in the distal ileum where they are known as Peyer's patches. When you consider that the alimentary canal is exposed to foodborne bacteria and other foreign matter, it is not hard to appreciate why the immune system has evolved a means of defending against the pathogens encountered within it.

Muscularis mucosa—This thin layer of smooth muscle is in a constant state of tension, pulling the mucosa of the stomach and small intestine into undulating folds. These folds dramatically increase the surface area available for digestion and absorption.

As its name implies, the **submucosa** lies immediately beneath the mucosa. A broad layer of dense connective tissue, it connects the overlying mucosa to the underlying muscularis. It includes blood and lymphatic vessels (which transport absorbed nutrients), and a scattering of submucosal glands that release digestive secretions. Additionally, it serves as a conduit for a dense branching network of nerves, the submucosal plexus, which functions as described below.

The third layer of the alimentary canal is the **muscularis** (also called the muscularis externa). The muscularis in the small intestine is made up of a double layer of smooth muscle: an inner circular layer and an outer longitudinal layer. The contractions of these layers promote mechanical digestion, expose more of the food to digestive chemicals, and move the food along the canal. In the most proximal and distal regions of the alimentary canal, including the mouth, pharynx, anterior part of the esophagus, and external anal sphincter, the muscularis is made up of skeletal muscle, which gives you voluntary control over swallowing and defecation. The basic two-layer structure found in the small intestine is modified in the organs proximal and distal to it. The stomach is equipped for its churning function by the addition of a third layer, the oblique muscle. While the colon has two layers like the small intestine, its longitudinal layer

is segregated into three narrow parallel bands, the tenia coli, which make it look like a series of pouches rather than a simple tube.

The **serosa** is the portion of the alimentary canal superficial to the muscularis. Present only in the region of the alimentary canal within the abdominal cavity, it consists of a layer of visceral peritoneum overlying a layer of loose connective tissue. Instead of serosa, the mouth, pharynx, and esophagus have a dense sheath of collagen fibers called the adventitia. These tissues serve to hold the alimentary canal in place near the ventral surface of the vertebral column.

Nerve Supply

As soon as food enters the mouth, it is detected by receptors that send impulses along the sensory neurons of cranial nerves. Without these nerves, not only would your food be without taste, but you would also be unable to feel either the food or the structures of your mouth, and you would be unable to avoid biting yourself as you chew, an action enabled by the motor branches of cranial nerves.

Intrinsic innervation of much of the alimentary canal is provided by the enteric nervous system, which runs from the esophagus to the anus, and contains approximately 100 million motor, sensory, and interneurons (unique to this system compared to all other parts of the peripheral nervous system). These enteric neurons are grouped into two plexuses. The **myenteric plexus** (plexus of Auerbach) lies in the muscularis layer of the alimentary canal and is responsible for **motility**, especially the rhythm and force of the contractions of the muscularis. The **submucosal plexus** (plexus of Meissner) lies in the submucosal layer and is responsible for regulating digestive secretions and reacting to the presence of food (see [\[link\]](#)).

Extrinsic innervations of the alimentary canal are provided by the autonomic nervous system, which includes both sympathetic and parasympathetic nerves. In general, sympathetic activation (the fight-or-flight response) restricts the activity of enteric neurons, thereby decreasing GI secretion and motility. In contrast, parasympathetic activation (the rest-

and-digest response) increases GI secretion and motility by stimulating neurons of the enteric nervous system.

Blood Supply

The blood vessels serving the digestive system have two functions. They transport the protein and carbohydrate nutrients absorbed by mucosal cells after food is digested in the lumen. Lipids are absorbed via lacteals, tiny structures of the lymphatic system. The blood vessels' second function is to supply the organs of the alimentary canal with the nutrients and oxygen needed to drive their cellular processes.

Specifically, the more anterior parts of the alimentary canal are supplied with blood by arteries branching off the aortic arch and thoracic aorta. Below this point, the alimentary canal is supplied with blood by arteries branching from the abdominal aorta. The celiac trunk services the liver, stomach, and duodenum, whereas the superior and inferior mesenteric arteries supply blood to the remaining small and large intestines.

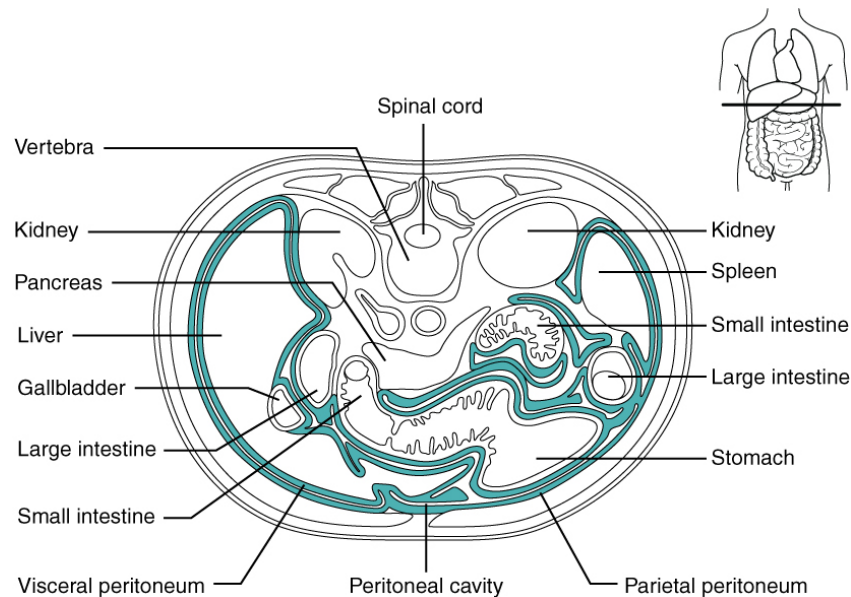
The veins that collect nutrient-rich blood from the small intestine (where most absorption occurs) empty into the hepatic portal system. This venous network takes the blood into the liver where the nutrients are either processed or stored for later use. Only then does the blood drained from the alimentary canal viscera circulate back to the heart. To appreciate just how demanding the digestive process is on the cardiovascular system, consider that while you are “resting and digesting,” about one-fourth of the blood pumped with each heartbeat enters arteries serving the intestines.

The Peritoneum

The digestive organs within the abdominal cavity are held in place by the peritoneum, a broad serous membranous sac made up of squamous epithelial tissue surrounded by connective tissue. It is composed of two different regions: the parietal peritoneum, which lines the abdominal wall, and the visceral peritoneum, which envelopes the abdominal organs ([\[link\]](#)). The peritoneal cavity is the space bounded by the visceral and parietal

peritoneal surfaces. A few milliliters of watery fluid act as a lubricant to minimize friction between the serosal surfaces of the peritoneum.

The Peritoneum



A cross-section of the abdomen shows the relationship between abdominal organs and the peritoneum (darker lines).

Note:

Disorders of the...

Digestive System: Peritonitis

Inflammation of the peritoneum is called peritonitis. Chemical peritonitis can develop any time the wall of the alimentary canal is breached, allowing the contents of the lumen entry into the peritoneal cavity. For example, when an ulcer perforates the stomach wall, gastric juices spill into the peritoneal cavity. Hemorrhagic peritonitis occurs after a ruptured tubal pregnancy or traumatic injury to the liver or spleen fills the peritoneal cavity with blood. Even more severe peritonitis is associated with bacterial infections seen with appendicitis, colonic diverticulitis, and pelvic inflammatory disease (infection of uterine tubes, usually by sexually

transmitted bacteria). Peritonitis is life threatening and often results in emergency surgery to correct the underlying problem and intensive antibiotic therapy. When your great grandparents and even your parents were young, the mortality from peritonitis was high. Aggressive surgery, improvements in anesthesia safety, the advance of critical care expertise, and antibiotics have greatly improved the mortality rate from this condition. Even so, the mortality rate still ranges from 30 to 40 percent.

The visceral peritoneum includes multiple large folds that envelope various abdominal organs, holding them to the dorsal surface of the body wall. Within these folds are blood vessels, lymphatic vessels, and nerves that innervate the organs with which they are in contact, supplying their adjacent organs. The five major peritoneal folds are described in [\[link\]](#). Note that during fetal development, certain digestive structures, including the first portion of the small intestine (called the duodenum), the pancreas, and portions of the large intestine (the ascending and descending colon, and the rectum) remain completely or partially posterior to the peritoneum. Thus, the location of these organs is described as **retroperitoneal**.

| The Five Major Peritoneal Folds | |
|---------------------------------|---|
| Fold | Description |
| Greater omentum | Apron-like structure that lies superficial to the small intestine and transverse colon; a site of fat deposition in people who are overweight |
| Falciform ligament | Anchors the liver to the anterior abdominal wall and inferior border of the diaphragm |

| The Five Major Peritoneal Folds | |
|---------------------------------|---|
| Fold | Description |
| Lesser omentum | Suspends the stomach from the inferior border of the liver; provides a pathway for structures connecting to the liver |
| Mesentery | Vertical band of tissue anterior to the lumbar vertebrae and anchoring all of the small intestine except the initial portion (the duodenum) |
| Mesocolon | Attaches two portions of the large intestine (the transverse and sigmoid colon) to the posterior abdominal wall |

Note:



By clicking on this [link](#) you can watch a short video of what happens to the food you eat, as it passes from your mouth to your intestine. Along the way, note how the food changes consistency and form. How does this change in consistency facilitate your gaining nutrients from food?

Chapter Review

The digestive system includes the organs of the alimentary canal and accessory structures. The alimentary canal forms a continuous tube that is

open to the outside environment at both ends. The organs of the alimentary canal are the mouth, pharynx, esophagus, stomach, small intestine, and large intestine. The accessory digestive structures include the teeth, tongue, salivary glands, liver, pancreas, and gallbladder. The wall of the alimentary canal is composed of four basic tissue layers: mucosa, submucosa, muscularis, and serosa. The enteric nervous system provides intrinsic innervation, and the autonomic nervous system provides extrinsic innervation.

Interactive Link Questions

Exercise:

Problem:

By clicking on this [link](#), you can watch a short video of what happens to the food you eat as it passes from your mouth to your intestine. Along the way, note how the food changes consistency and form. How does this change in consistency facilitate your gaining nutrients from food?

Solution:

Answers may vary.

Review Questions

Exercise:

Problem:

Which of these organs is not considered an accessory digestive structure?

- a. mouth
- b. salivary glands
- c. pancreas
- d. liver

Solution:

A

Exercise:

Problem:

Which of the following organs is supported by a layer of adventitia rather than serosa?

- a. esophagus
- b. stomach
- c. small intestine
- d. large intestine

Solution:

A

Exercise:

Problem: Which of the following membranes covers the stomach?

- a. falciform ligament
- b. mesocolon
- c. parietal peritoneum
- d. visceral peritoneum

Solution:

D

Critical Thinking Questions

Exercise:**Problem:**

Explain how the enteric nervous system supports the digestive system. What might occur that could result in the autonomic nervous system having a negative impact on digestion?

Solution:

The enteric nervous system helps regulate alimentary canal motility and the secretion of digestive juices, thus facilitating digestion. If a person becomes overly anxious, sympathetic innervation of the alimentary canal is stimulated, which can result in a slowing of digestive activity.

Exercise:**Problem:**

What layer of the alimentary canal tissue is capable of helping to protect the body against disease, and through what mechanism?

Solution:

The lamina propria of the mucosa contains lymphoid tissue that makes up the MALT and responds to pathogens encountered in the alimentary canal.

Glossary

accessory digestive organ

includes teeth, tongue, salivary glands, gallbladder, liver, and pancreas

alimentary canal

continuous muscular digestive tube that extends from the mouth to the anus

motility

movement of food through the GI tract

mucosa

innermost lining of the alimentary canal

muscularis

muscle (skeletal or smooth) layer of the alimentary canal wall

myenteric plexus

(plexus of Auerbach) major nerve supply to alimentary canal wall;
controls motility

retroperitoneal

located posterior to the peritoneum

serosa

outermost layer of the alimentary canal wall present in regions within
the abdominal cavity

submucosa

layer of dense connective tissue in the alimentary canal wall that binds
the overlying mucosa to the underlying muscularis

submucosal plexus

(plexus of Meissner) nerve supply that regulates activity of glands and
smooth muscle

Digestive System Processes and Regulation

By the end of this section, you will be able to:

- Discuss six fundamental activities of the digestive system, giving an example of each
- Compare and contrast the neural and hormonal controls involved in digestion

The digestive system uses mechanical and chemical activities to break food down into absorbable substances during its journey through the digestive system. [\[link\]](#) provides an overview of the basic functions of the digestive organs.

Note:



Visit this [site](#) for an overview of digestion of food in different regions of the digestive tract. Note the route of non-fat nutrients from the small intestine to their release as nutrients to the body.

| Functions of the Digestive Organs | | |
|-----------------------------------|-----------------|-----------------|
| Organ | Major functions | Other functions |

| Functions of the Digestive Organs | | |
|-----------------------------------|--|---|
| Organ | Major functions | Other functions |
| Mouth | Ingests food Chews and mixes food Begins chemical breakdown of carbohydrates Moves food into the pharynx Begins breakdown of lipids via lingual lipase | Moistens and dissolves food, allowing you to taste it Cleans and lubricates the teeth and oral cavity Has some antimicrobial activity |
| Pharynx | Propels food from the oral cavity to the esophagus | Lubricates food and passageways |
| Esophagus | Propels food to the stomach | Lubricates food and passageways |

| Functions of the Digestive Organs | | |
|-----------------------------------|---|--|
| Organ | Major functions | Other functions |
| Stomach | <p>Mixes and churns food with gastric juices to form chyme</p> <p>Begins chemical breakdown of proteins</p> <p>Releases food into the duodenum as chyme</p> <p>Absorbs some fat-soluble substances (for example, alcohol, aspirin)</p> <p>Possesses antimicrobial functions</p> | <p>Stimulates protein-digesting enzymes</p> <p>Secretes intrinsic factor required for vitamin B₁₂ absorption in small intestine</p> |

| Functions of the Digestive Organs | | |
|-----------------------------------|---|---|
| Organ | Major functions | Other functions |
| Small intestine | <p>Mixes chyme with digestive juices</p> <p>Propels food at a rate slow enough for digestion and absorption</p> <p>Absorbs breakdown products of carbohydrates, proteins, lipids, and nucleic acids, along with vitamins, minerals, and water</p> <p>Performs physical digestion via segmentation</p> | <p>Provides optimal medium for enzymatic activity</p> |

| Functions of the Digestive Organs | | |
|-----------------------------------|---|--|
| Organ | Major functions | Other functions |
| Accessory organs | <p>Liver: produces bile salts, which emulsify lipids, aiding their digestion and absorption</p> <p>Gallbladder: stores, concentrates, and releases bile</p> <p>Pancreas: produces digestive enzymes and bicarbonate</p> | <p>Bicarbonate-rich pancreatic juices help neutralize acidic chyme and provide optimal environment for enzymatic activity</p> |
| Large intestine | <p>Further breaks down food residues</p> <p>Absorbs most residual water, electrolytes, and vitamins produced by enteric bacteria</p> <p>Propels feces toward rectum</p> <p>Eliminates feces</p> | <p>Food residue is concentrated and temporarily stored prior to defecation</p> <p>Mucus eases passage of feces through colon</p> |

Digestive Processes

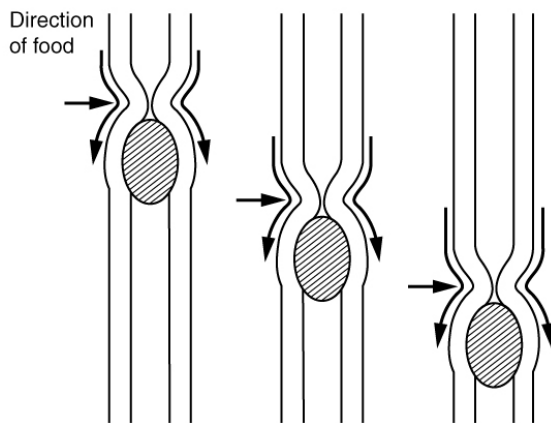
The processes of digestion include six activities: ingestion, propulsion, mechanical or physical digestion, chemical digestion, absorption, and

defecation.

The first of these processes, **ingestion**, refers to the entry of food into the alimentary canal through the mouth. There, the food is chewed and mixed with saliva, which contains enzymes that begin breaking down the carbohydrates in the food plus some lipid digestion via lingual lipase. Chewing increases the surface area of the food and allows an appropriately sized bolus to be produced.

Food leaves the mouth when the tongue and pharyngeal muscles propel it into the esophagus. This act of swallowing, the last voluntary act until defecation, is an example of **propulsion**, which refers to the movement of food through the digestive tract. It includes both the voluntary process of swallowing and the involuntary process of peristalsis. **Peristalsis** consists of sequential, alternating waves of contraction and relaxation of alimentary wall smooth muscles, which act to propel food along ([link](#)). These waves also play a role in mixing food with digestive juices. Peristalsis is so powerful that foods and liquids you swallow enter your stomach even if you are standing on your head.

Peristalsis



Peristalsis moves food through the digestive tract with alternating waves of muscle contraction and relaxation.

Digestion includes both mechanical and chemical processes. **Mechanical digestion** is a purely physical process that does not change the chemical nature of the food. Instead, it makes the food smaller to increase both surface area and mobility. It includes **mastication**, or chewing, as well as tongue movements that help break food into smaller bits and mix food with saliva. Although there may be a tendency to think that mechanical digestion is limited to the first steps of the digestive process, it occurs after the food leaves the mouth, as well. The mechanical churning of food in the stomach serves to further break it apart and expose more of its surface area to digestive juices, creating an acidic “soup” called **chyme**. **Segmentation**, which occurs mainly in the small intestine, consists of localized contractions of circular muscle of the muscularis layer of the alimentary canal. These contractions isolate small sections of the intestine, moving their contents back and forth while continuously subdividing, breaking up, and mixing the contents. By moving food back and forth in the intestinal lumen, segmentation mixes food with digestive juices and facilitates absorption.

In **chemical digestion**, starting in the mouth, digestive secretions break down complex food molecules into their chemical building blocks (for example, proteins into separate amino acids). These secretions vary in composition, but typically contain water, various enzymes, acids, and salts. The process is completed in the small intestine.

Food that has been broken down is of no value to the body unless it enters the bloodstream and its nutrients are put to work. This occurs through the process of **absorption**, which takes place primarily within the small intestine. There, most nutrients are absorbed from the lumen of the alimentary canal into the bloodstream through the epithelial cells that make up the mucosa. Lipids are absorbed into lacteals and are transported via the lymphatic vessels to the bloodstream (the subclavian veins near the heart). The details of these processes will be discussed later.

In **defecation**, the final step in digestion, undigested materials are removed from the body as feces.

Note:

Aging and the...

Digestive System: From Appetite Suppression to Constipation

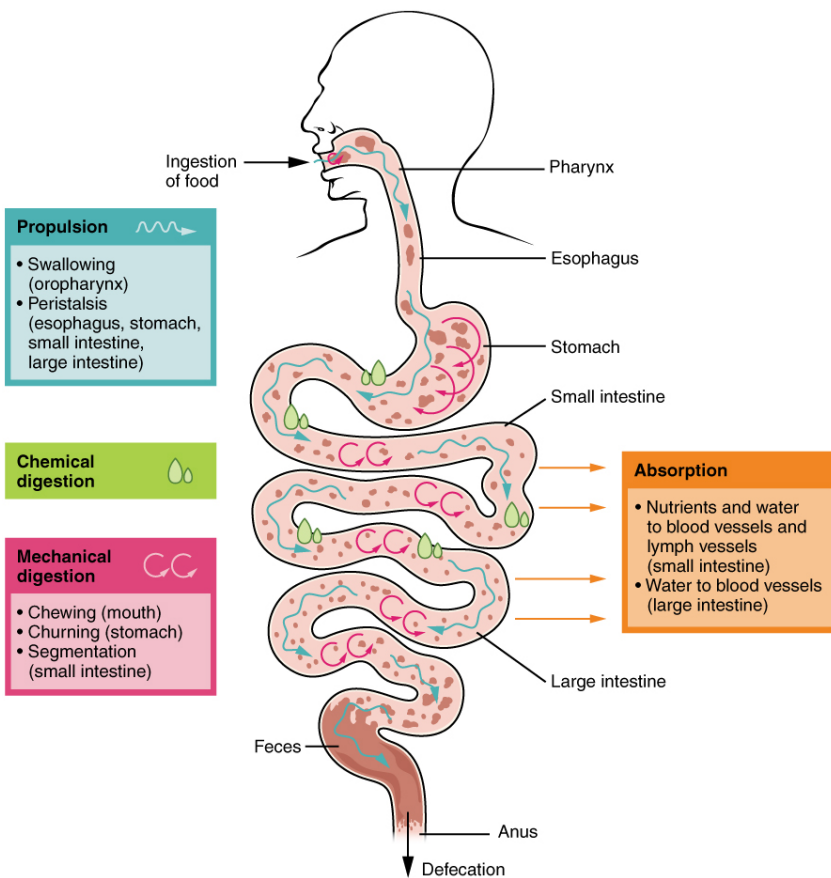
Age-related changes in the digestive system begin in the mouth and can affect virtually every aspect of the digestive system. Taste buds become less sensitive, so food isn't as appetizing as it once was. A slice of pizza is a challenge, not a treat, when you have lost teeth, your gums are diseased, and your salivary glands aren't producing enough saliva. Swallowing can be difficult, and ingested food moves slowly through the alimentary canal because of reduced strength and tone of muscular tissue. Neurosensory feedback is also dampened, slowing the transmission of messages that stimulate the release of enzymes and hormones.

Pathologies that affect the digestive organs—such as hiatal hernia, gastritis, and peptic ulcer disease—can occur at greater frequencies as you age.

Problems in the small intestine may include duodenal ulcers, maldigestion, and malabsorption. Problems in the large intestine include hemorrhoids, diverticular disease, and constipation. Conditions that affect the function of accessory organs—and their abilities to deliver pancreatic enzymes and bile to the small intestine—include jaundice, acute pancreatitis, cirrhosis, and gallstones.

In some cases, a single organ is in charge of a digestive process. For example, ingestion occurs only in the mouth and defecation only in the anus. However, most digestive processes involve the interaction of several organs and occur gradually as food moves through the alimentary canal ([link](#)).

Digestive Processes



The digestive processes are ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation.

Some chemical digestion occurs in the mouth. Some absorption can occur in the mouth and stomach, for example, alcohol and aspirin.

Regulatory Mechanisms

Neural and endocrine regulatory mechanisms work to maintain the optimal conditions in the lumen needed for digestion and absorption. These regulatory mechanisms, which stimulate digestive activity through mechanical and chemical activity, are controlled both extrinsically and intrinsically.

Neural Controls

The walls of the alimentary canal contain a variety of sensors that help regulate digestive functions. These include mechanoreceptors, chemoreceptors, and osmoreceptors, which are capable of detecting mechanical, chemical, and osmotic stimuli, respectively. For example, these receptors can sense when the presence of food has caused the stomach to expand, whether food particles have been sufficiently broken down, how much liquid is present, and the type of nutrients in the food (lipids, carbohydrates, and/or proteins). Stimulation of these receptors provokes an appropriate reflex that furthers the process of digestion. This may entail sending a message that activates the glands that secrete digestive juices into the lumen, or it may mean the stimulation of muscles within the alimentary canal, thereby activating peristalsis and segmentation that move food along the intestinal tract.

The walls of the entire alimentary canal are embedded with nerve plexuses that interact with the central nervous system and other nerve plexuses—either within the same digestive organ or in different ones. These interactions prompt several types of reflexes. Extrinsic nerve plexuses orchestrate long reflexes, which involve the central and autonomic nervous systems and work in response to stimuli from outside the digestive system. Short reflexes, on the other hand, are orchestrated by intrinsic nerve plexuses within the alimentary canal wall. These two plexuses and their connections were introduced earlier as the enteric nervous system. Short reflexes regulate activities in one area of the digestive tract and may coordinate local peristaltic movements and stimulate digestive secretions. For example, the sight, smell, and taste of food initiate long reflexes that begin with a sensory neuron delivering a signal to the medulla oblongata. The response to the signal is to stimulate cells in the stomach to begin secreting digestive juices in preparation for incoming food. In contrast, food that distends the stomach initiates short reflexes that cause cells in the stomach wall to increase their secretion of digestive juices.

Hormonal Controls

A variety of hormones are involved in the digestive process. The main digestive hormone of the stomach is gastrin, which is secreted in response to the presence of food. Gastrin stimulates the secretion of gastric acid by the parietal cells of the stomach mucosa. Other GI hormones are produced and act upon the gut and its accessory organs. Hormones produced by the duodenum include secretin, which stimulates a watery secretion of bicarbonate by the pancreas; cholecystokinin (CCK), which stimulates the secretion of pancreatic enzymes and bile from the liver and release of bile from the gallbladder; and gastric inhibitory peptide, which inhibits gastric secretion and slows gastric emptying and motility. These GI hormones are secreted by specialized epithelial cells, called endocrinocytes, located in the mucosal epithelium of the stomach and small intestine. These hormones then enter the bloodstream, through which they can reach their target organs.

Chapter Review

The digestive system ingests and digests food, absorbs released nutrients, and excretes food components that are indigestible. The six activities involved in this process are ingestion, motility, mechanical digestion, chemical digestion, absorption, and defecation. These processes are regulated by neural and hormonal mechanisms.

Interactive Link Questions

Exercise:

Problem:

Visit this [site](#) for an overview of digestion of food in different regions of the digestive tract. Note the route of non-fat nutrients from the small intestine to their release as nutrients to the body.

Solution:

Answers may vary.

Multiple Choice

Exercise:

Problem: Which of these processes occurs in the mouth?

- a. ingestion
- b. mechanical digestion
- c. chemical digestion
- d. all of the above

Solution:

D

Exercise:

Problem:

Which of these processes occurs throughout most of the alimentary canal?

- a. ingestion
- b. propulsion
- c. segmentation
- d. absorption

Solution:

B

Exercise:

Problem:

Which of the following stimuli activates sensors in the walls of digestive organs?

- a. breakdown products of digestion
 - b. distension
 - c. pH of chyme
 - d. all of the above
-

Solution:

D

Exercise:

Problem:

Which of these statements about reflexes in the GI tract is false?

- a. Short reflexes are provoked by nerves near the GI tract.
 - b. Short reflexes are mediated by the enteric nervous system.
 - c. Food that distends the stomach initiates long reflexes.
 - d. Long reflexes can be provoked by stimuli originating outside the GI tract.
-

Solution:

C

Critical Thinking Questions

Exercise:

Problem:

Offer a theory to explain why segmentation occurs and peristalsis slows in the small intestine.

Solution:

The majority of digestion and absorption occurs in the small intestine. By slowing the transit of chyme, segmentation and a reduced rate of peristalsis allow time for these processes to occur.

Exercise:

Problem:

It has been several hours since you last ate. Walking past a bakery, you catch a whiff of freshly baked bread. What type of reflex is triggered, and what is the result?

Solution:

The smell of food initiates long reflexes, which result in the secretion of digestive juices.

Glossary

absorption

passage of digested products from the intestinal lumen through mucosal cells and into the bloodstream or lacteals

chemical digestion

enzymatic breakdown of food

chyme

soupy liquid created when food is mixed with digestive juices

defecation

elimination of undigested substances from the body in the form of feces

ingestion

taking food into the GI tract through the mouth

mastication

chewing

mechanical digestion

chewing, mixing, and segmentation that prepares food for chemical digestion

peristalsis

muscular contractions and relaxations that propel food through the GI tract

propulsion

voluntary process of swallowing and the involuntary process of peristalsis that moves food through the digestive tract

segmentation

alternating contractions and relaxations of non-adjacent segments of the intestine that move food forward and backward, breaking it apart and mixing it with digestive juices

The Mouth, Pharynx, and Esophagus

By the end of this section, you will be able to:

- Describe the structures of the mouth, including its three accessory digestive organs
- Group the 32 adult teeth according to name, location, and function
- Describe the process of swallowing, including the roles of the tongue, upper esophageal sphincter, and epiglottis
- Trace the pathway food follows from ingestion into the mouth through release into the stomach

In this section, you will examine the anatomy and functions of the three main organs of the upper alimentary canal—the mouth, pharynx, and esophagus—as well as three associated accessory organs—the tongue, salivary glands, and teeth.

The Mouth

The cheeks, tongue, and palate frame the mouth, which is also called the **oral cavity** (or buccal cavity). The structures of the mouth are illustrated in [\[link\]](#).

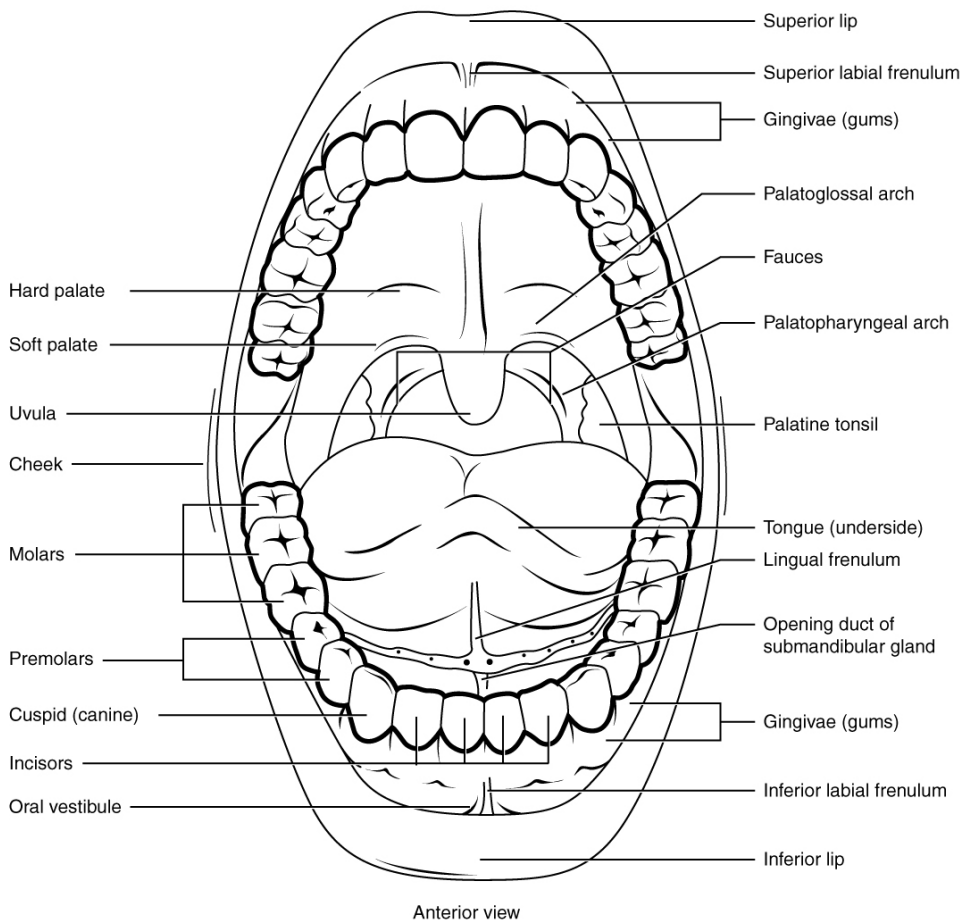
At the entrance to the mouth are the lips, or **labia** (singular = labium). Their outer covering is skin, which transitions to a mucous membrane in the mouth proper. Lips are very vascular with a thin layer of keratin; hence, the reason they are "red." They have a huge representation on the cerebral cortex, which probably explains the human fascination with kissing! The lips cover the orbicularis oris muscle, which regulates what comes in and goes out of the mouth. The **labial frenulum** is a midline fold of mucous membrane that attaches the inner surface of each lip to the gum. The cheeks make up the oral cavity's sidewalls. While their outer covering is skin, their inner covering is mucous membrane. This membrane is made up of non-keratinized, stratified squamous epithelium. Between the skin and mucous membranes are connective tissue and buccinator muscles. The next time you eat some food, notice how the buccinator muscles in your cheeks and the orbicularis oris muscle in your lips contract, helping you keep the food

from falling out of your mouth. Additionally, notice how these muscles work when you are speaking.

The pocket-like part of the mouth that is framed on the inside by the gums and teeth, and on the outside by the cheeks and lips is called the **oral vestibule**. Moving farther into the mouth, the opening between the oral cavity and throat (oropharynx) is called the **fauces** (like the kitchen "faucet"). The main open area of the mouth, or oral cavity proper, runs from the gums and teeth to the fauces.

When you are chewing, you do not find it difficult to breathe simultaneously. The next time you have food in your mouth, notice how the arched shape of the roof of your mouth allows you to handle both digestion and respiration at the same time. This arch is called the palate. The anterior region of the palate serves as a wall (or septum) between the oral and nasal cavities as well as a rigid shelf against which the tongue can push food. It is created by the maxillary and palatine bones of the skull and, given its bony structure, is known as the hard palate. If you run your tongue along the roof of your mouth, you'll notice that the hard palate ends in the posterior oral cavity, and the tissue becomes fleshier. This part of the palate, known as the **soft palate**, is composed mainly of skeletal muscle. You can therefore manipulate, subconsciously, the soft palate—for instance, to yawn, swallow, or sing (see [\[link\]](#)).

Mouth



The mouth includes the lips, tongue, palate, gums, and teeth.

A fleshy bead of tissue called the uvula drops down from the center of the posterior edge of the soft palate. Although some have suggested that the uvula is a vestigial organ, it serves an important purpose. When you swallow, the soft palate and uvula move upward, helping to keep foods and liquid from entering the nasal cavity. Unfortunately, it can also contribute to the sound produced by snoring. Two muscular folds extend downward from the soft palate, on either side of the uvula. Toward the front, the **palatoglossal arch** lies next to the base of the tongue; behind it, the **palatopharyngeal arch** forms the superior and lateral margins of the fauces. Between these two arches are the palatine tonsils, clusters of

lymphoid tissue that protect the pharynx. The lingual tonsils are located at the base of the tongue.

The Tongue

Perhaps you have heard it said that the **tongue** is the strongest muscle in the body. Those who stake this claim cite its strength proportionate to its size. Although it is difficult to quantify the relative strength of different muscles, it remains indisputable that the tongue is a workhorse, facilitating ingestion, mechanical digestion, chemical digestion (lingual lipase), sensation (of taste, texture, and temperature of food), swallowing, and vocalization.

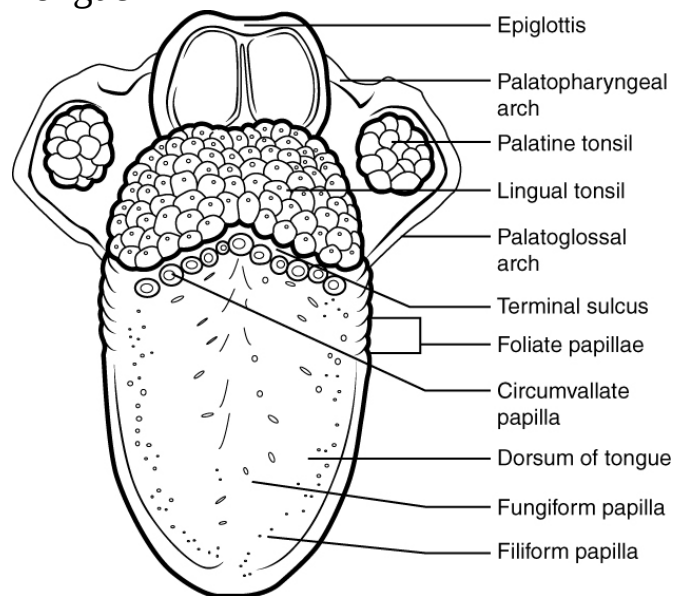
The tongue is attached to the mandible, the styloid processes of the temporal bones, and the hyoid bone. The hyoid is unique in that it only distantly/indirectly articulates with other bones. The tongue is positioned over the floor of the oral cavity. A medial septum extends the entire length of the tongue, dividing it into symmetrical halves.

Beneath its mucous membrane covering, each half of the tongue is composed of the same number and type of intrinsic and extrinsic skeletal muscles. The intrinsic muscles (those within the tongue) are the longitudinalis inferior, longitudinalis superior, transversus linguae, and verticalis linguae muscles. These allow you to change the size and shape of your tongue, as well as to stick it out, if you wish. Having such a flexible tongue facilitates both swallowing and speech.

As you learned in your study of the muscular system, the extrinsic muscles of the tongue are the mylohyoid, hyoglossus, styloglossus, and genioglossus muscles. These muscles originate outside the tongue and insert into connective tissues within the tongue. The mylohyoid is responsible for raising the tongue, the hyoglossus pulls it down and back, the styloglossus pulls it up and back, and the genioglossus pulls it forward. Working in concert, these muscles perform three important digestive functions in the mouth: (1) position food for optimal chewing, (2) gather food into a **bolus** (rounded mass), and (3) position food so it can be swallowed.

The top and sides of the tongue are studded with papillae, extensions of lamina propria of the mucosa, which are covered in stratified squamous epithelium ([link](#)). Fungiform papillae, which are mushroom shaped, cover a large area of the tongue; they tend to be larger toward the rear of the tongue and smaller on the tip and sides. In contrast, filiform papillae are long and thin. Fungiform papillae contain taste buds, and filiform papillae have touch receptors that help the tongue move food around in the mouth. The filiform papillae create an abrasive surface that performs mechanically, much like a cat's rough tongue that is used for grooming. Lingual glands in the lamina propria of the tongue secrete mucus and a watery serous fluid that contains the enzyme **lingual lipase**, which plays a minor role in breaking down triglycerides but does not begin working until it is activated in the stomach. A fold of mucous membrane on the underside of the tongue, the **lingual frenulum**, tethers the tongue to the floor of the mouth. People with the congenital anomaly ankyloglossia, also known by the non-medical term "tongue tie," have a lingual frenulum that is too short or otherwise malformed. Severe ankyloglossia can impair speech and must be corrected with surgery.

Tongue



This superior view of the tongue shows the locations and types of lingual papillae.

The Salivary Glands

Many small **salivary glands** are housed within the mucous membranes of the mouth and tongue. These minor exocrine glands are constantly secreting saliva, either directly into the oral cavity or indirectly through ducts, even while you sleep. In fact, an average of 1 to 1.5 liters of saliva is secreted each day. Usually just enough saliva is present to moisten the mouth and teeth. Secretion increases when you eat, because saliva is essential to moisten food and initiate the chemical breakdown of carbohydrates. Small amounts of saliva are also secreted by the labial glands in the lips. In addition, the buccal glands in the cheeks, palatal glands in the palate, and lingual glands in the tongue help ensure that all areas of the mouth are supplied with adequate saliva.

The Major Salivary Glands

Outside the oral mucosa are three pairs of major salivary glands, which secrete the majority of saliva into ducts that open into the mouth:

- The **submandibular glands**, which are in the floor of the mouth, secrete saliva into the mouth through the submandibular ducts.
- The **sublingual glands**, which lie below the tongue, use the lesser sublingual ducts to secrete saliva into the oral cavity.
- The **parotid glands** lie between the skin and the masseter muscle, near the ears. They secrete saliva into the mouth through the parotid duct, which is located near the second upper molar tooth ([\[link\]](#)).

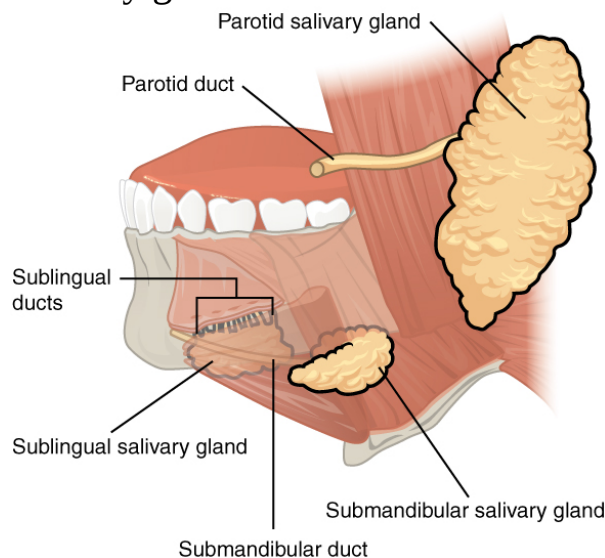
Saliva

Saliva is essentially (98 to 99.5 percent) water. The remaining 4.5 percent is a complex mixture of ions, glycoproteins, enzymes, growth factors, and waste products. Perhaps the most important ingredient in saliva from the

perspective of digestion is the enzyme **salivary amylase**, which initiates the breakdown of carbohydrates. Food does not spend enough time in the mouth to allow all the carbohydrates to break down, but salivary amylase continues acting until it is inactivated by stomach acids. Bicarbonate and phosphate ions function as chemical buffers, maintaining saliva at a pH between 6.35 and 6.85. Salivary mucus helps lubricate food, facilitating movement in the mouth, bolus formation, and swallowing. Saliva contains immunoglobulin A, which prevents microbes from penetrating the epithelium, and lysozyme, which makes saliva antimicrobial. Saliva also contains epidermal growth factor, which might have given rise to the adage “a mother’s kiss can heal a wound.”

Each of the major salivary glands secretes a unique formulation of saliva according to its cellular makeup. For example, the parotid glands secrete a watery solution that contains salivary amylase. The submandibular glands have cells similar to those of the parotid glands, as well as mucus-secreting cells. Therefore, saliva secreted by the submandibular glands also contains amylase but in a liquid thickened with mucus. The sublingual glands contain mostly mucous cells, and they secrete the thickest saliva with the least amount of salivary amylase.

Salivary glands



The major salivary glands are located outside the oral mucosa

and deliver saliva into the mouth through ducts.

Note:

Homeostatic Imbalances

The Parotid Glands: Mumps

Infections of the nasal passages and pharynx can attack any salivary gland. The parotid glands are the usual site of infection with the virus that causes mumps (paramyxovirus). Mumps manifests by enlargement and inflammation of the parotid glands, causing a characteristic swelling between the ears and the jaw. Symptoms include fever and throat pain, which can be severe when swallowing acidic substances such as orange juice.

In about one-third of men who are past puberty, mumps also causes testicular inflammation, typically affecting only one testis and rarely resulting in sterility. With the increasing use and effectiveness of mumps vaccines, the incidence of mumps has decreased dramatically. According to the U.S. Centers for Disease Control and Prevention (CDC), the number of mumps cases dropped from more than 150,000 in 1968 to fewer than 1700 in 1993 to only 11 reported cases in 2011.

Regulation of Salivation

The autonomic nervous system regulates **salivation** (the secretion of saliva). In the absence of food, parasympathetic stimulation keeps saliva flowing at just the right level for comfort as you speak, swallow, sleep, and generally go about life. Over-salivation can occur, for example, if you are stimulated by the smell of food, but that food is not available for you to eat. Drooling is an extreme instance of the overproduction of saliva. During times of stress, such as before speaking in public, sympathetic stimulation takes over, reducing salivation and producing the symptom of dry mouth often associated with anxiety. When you are dehydrated, salivation is

reduced, causing the mouth to feel dry and prompting you to take action to quench your thirst.

Salivation can be stimulated by the sight, smell, and taste of food. It can even be stimulated by thinking about food. You might notice whether reading about food and salivation right now has had any effect on your production of saliva.

How does the salivation process work while you are eating? Food contains chemicals that stimulate taste receptors on the tongue, which send impulses to the superior and inferior salivatory nuclei in the brain stem. These two nuclei then send back parasympathetic impulses through fibers in the glossopharyngeal and facial nerves, which stimulate salivation. Even after you swallow food, salivation is increased to cleanse the mouth and to water down and neutralize any irritating chemical remnants, such as that hot sauce in your burrito. Most saliva is swallowed along with food and is reabsorbed, so that fluid is not lost.

The Teeth

The teeth, or **dentes** (singular = dens), are organs similar to bones that you use to tear, grind, and otherwise mechanically break down food.

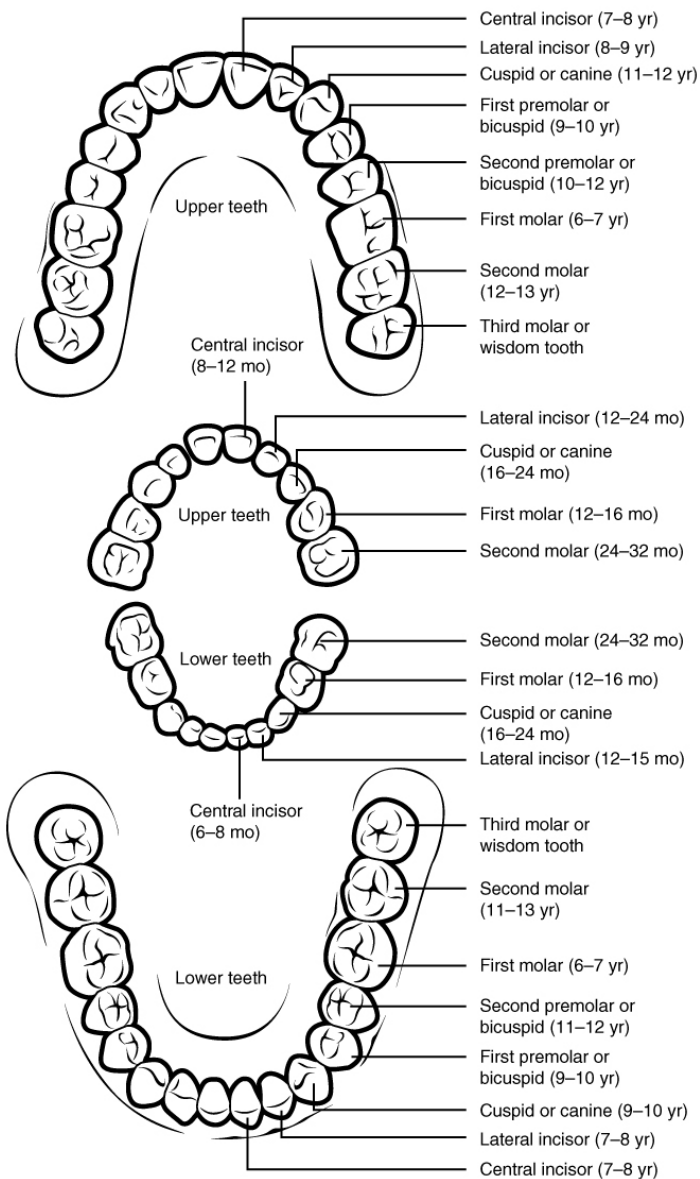
Types of Teeth

During the course of your lifetime, you have two sets of teeth (one set of teeth is a **dentition**). Your 20 **deciduous teeth**, or baby teeth, first begin to appear at about 6 months of age. Between approximately age 6 and 12, these teeth are replaced by 32 **permanent teeth**. Moving from the center of the mouth toward the side, these are as follows ([link](#)):

- The eight **incisors**, four top and four bottom, are the sharp front teeth you use for biting into food.
- The four **cuspids** (or canines) flank the incisors and have a pointed edge (cusp) to tear up food. These fang-like teeth are superb for piercing tough or fleshy foods.

- Posterior to the cuspids are the eight **premolars** (or bicuspid), which have an overall flatter shape with two rounded cusps useful for mashing foods.
- The most posterior and largest are the 12 **molars**, which have several pointed cusps used to crush food so it is ready for swallowing. The third members of each set of three molars, top and bottom, are commonly referred to as the wisdom teeth, because their eruption is commonly delayed until early adulthood. It is not uncommon for wisdom teeth to fail to erupt; that is, they remain impacted. In these cases, the teeth are typically removed by orthodontic surgery.

Permanent and Deciduous Teeth



This figure of two human dentitions shows the arrangement of teeth in the maxilla and mandible, and the relationship between the deciduous and permanent teeth.

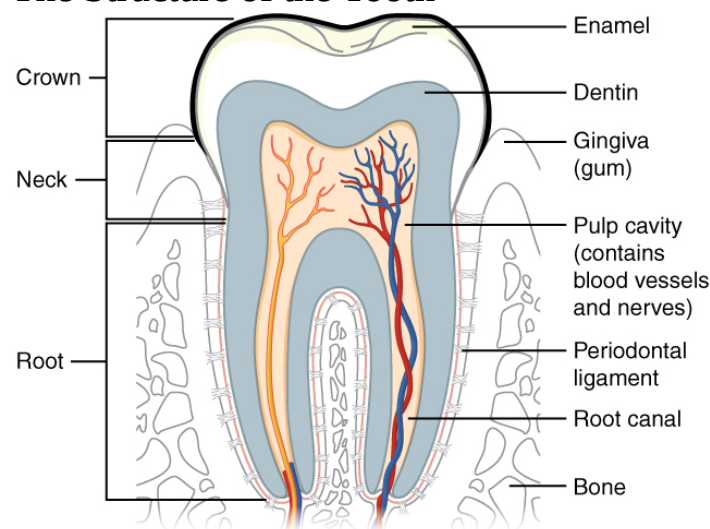
Anatomy of a Tooth

The teeth are secured in the alveolar processes (sockets) of the maxilla and the mandible. **Gingivae** (commonly called the gums) are soft tissues that line the alveolar processes and surround the necks of the teeth. Teeth are also held in their sockets by a connective tissue called the periodontal ligament.

The two main parts of a tooth are the **crown**, which is the portion projecting above the gum line, and the **root**, which is embedded within the maxilla and mandible. Both parts contain an inner **pulp cavity**, containing loose connective tissue through which run nerves and blood vessels. The region of the pulp cavity that runs through the root of the tooth is called the root canal. Surrounding the pulp cavity is **dentin**, a bone-like tissue. In the root of each tooth, the dentin is covered by an even harder bone-like layer called **cementum**. In the crown of each tooth, the dentin is covered by an outer layer of **enamel**, the hardest substance in the body ([\[link\]](#)).

Although enamel protects the underlying dentin and pulp cavity, it is still nonetheless susceptible to mechanical and chemical erosion, or what is known as tooth decay. The most common form, dental caries (cavities) develops when colonies of bacteria feeding on sugars in the mouth release acids that cause soft tissue inflammation and degradation of the calcium crystals of the enamel. The digestive functions of the mouth are summarized in [\[link\]](#).

The Structure of the Tooth



This longitudinal section through a

molar in its alveolar socket shows the relationships between enamel, dentin, and pulp.

| Digestive Functions of the Mouth | | |
|----------------------------------|--------------------------------------|---|
| Structure | Action | Outcome |
| Lips and cheeks | Confine food between teeth | Food is chewed evenly during mastication |
| Salivary glands | Secrete saliva | Moisten and lubricate the lining of the mouth and pharynx Moisten, soften, and dissolve food Clean the mouth and teeth Salivary amylase breaks down starch |
| Tongue's extrinsic muscles | Move tongue sideways, and in and out | Manipulate food for chewing Shape food into a bolus Manipulate food for swallowing |

| Digestive Functions of the Mouth | | |
|---|-------------------------------------|---|
| Structure | Action | Outcome |
| Tongue's intrinsic muscles | Change tongue shape | Manipulate food for swallowing |
| Taste buds | Sense food in mouth and sense taste | Nerve impulses from taste buds are conducted to salivary nuclei in the brain stem and then to salivary glands, stimulating saliva secretion |
| Lingual glands | Secrete lingual lipase | Activated in the stomach Break down triglycerides into fatty acids and diglycerides |
| Teeth | Shred and crush food | Break down solid food into smaller particles for deglutition |

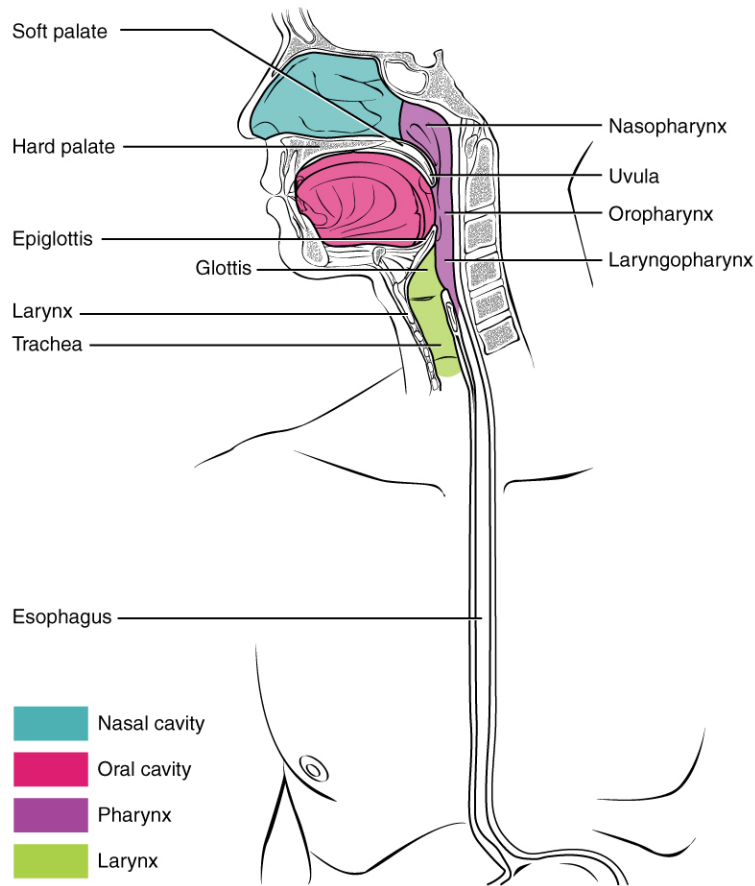
The Pharynx

The **pharynx** (throat) is involved in both digestion and respiration. It receives food and air from the mouth, and air from the nasal cavities. When food enters the pharynx, involuntary muscle contractions close off the air passageways.

A short tube of skeletal muscle lined with a mucous membrane, the pharynx runs from the posterior oral and nasal cavities to the opening of the esophagus and larynx. It has three subdivisions. The most superior, the

nasopharynx, is involved only in breathing and speech. The other two subdivisions, the **oropharynx** and the **laryngopharynx**, are used for both breathing and digestion. The oropharynx begins inferior to the nasopharynx and is continuous below with the laryngopharynx ([\[link\]](#)). The inferior border of the laryngopharynx connects to the esophagus, whereas the anterior portion connects to the larynx, allowing air to flow into the bronchial tree.

Pharynx



The pharynx runs from the nostrils to the esophagus and the larynx.

Histologically, the wall of the oropharynx is similar to that of the oral cavity. The mucosa includes a stratified squamous epithelium that is endowed with mucus-producing glands. During swallowing, the elevator skeletal muscles of the pharynx contract, raising and expanding the pharynx

to receive the bolus of food. Once received, these muscles relax and the constrictor muscles of the pharynx contract, forcing the bolus into the esophagus and initiating peristalsis.

Usually during swallowing, the soft palate and uvula rise reflexively to close off the entrance to the nasopharynx. At the same time, the larynx is pulled superiorly and the cartilaginous epiglottis, its most superior structure, folds inferiorly, covering the glottis (the opening to the larynx); this process effectively blocks access to the trachea and bronchi. When the food “goes down the wrong way,” it goes into the trachea. When food enters the trachea, the reaction is to cough, which usually forces the food up and out of the trachea, and back into the pharynx.

The Esophagus

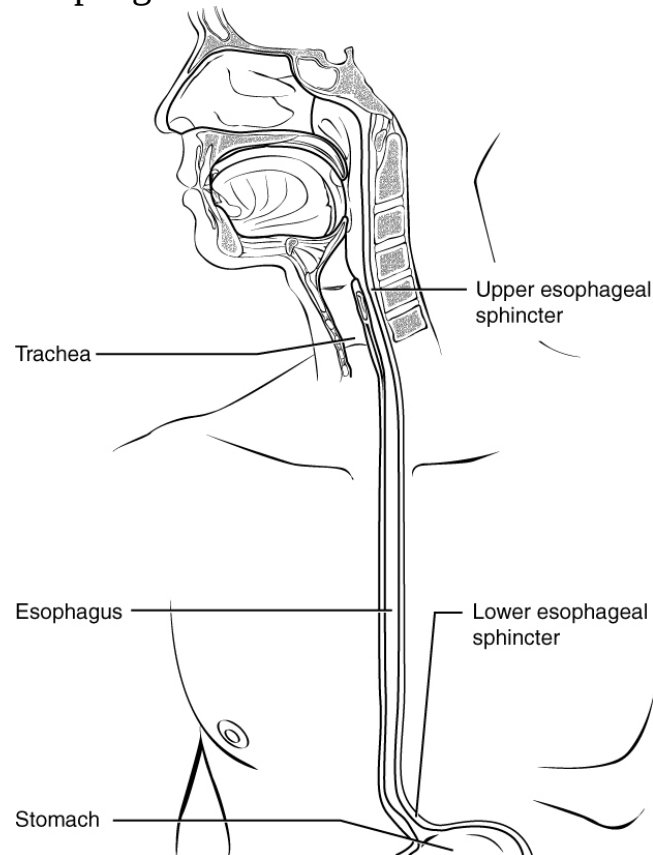
The **esophagus** is a muscular tube that connects the pharynx to the stomach. It is approximately 25.4 cm (10 in) in length, located posterior to the trachea, and remains in a collapsed form when not engaged in swallowing. As you can see in [\[link\]](#), the esophagus runs a mainly straight route through the mediastinum of the thorax. To enter the abdomen, the esophagus penetrates the diaphragm through an opening called the esophageal hiatus.

Passage of Food through the Esophagus

The **upper esophageal sphincter**, which is continuous with the inferior pharyngeal constrictor, controls the movement of food from the pharynx into the esophagus. The upper two-thirds of the esophagus consists of both smooth and skeletal muscle fibers, with the latter fading out in the bottom third of the esophagus. Rhythmic waves of peristalsis, which begin in the upper esophagus, propel the bolus of food toward the stomach. Meanwhile, secretions from the esophageal mucosa lubricate the esophagus and food. Food passes from the esophagus into the stomach at the **lower esophageal sphincter** (also called the gastroesophageal or cardiac sphincter). Recall that sphincters are muscles that surround tubes and serve as valves, closing the tube when the sphincters contract and opening it when they relax. The

lower esophageal sphincter relaxes to let food pass into the stomach, and then contracts to prevent stomach acids from backing up into the esophagus. Surrounding this sphincter is the muscular diaphragm, which helps close off the sphincter when no food is being swallowed. When the lower esophageal sphincter does not completely close, the stomach's contents can reflux (that is, back up into the esophagus), causing heartburn or gastroesophageal reflux disease (GERD).

Esophagus



The upper esophageal sphincter controls the movement of food from the pharynx to the esophagus. The lower esophageal sphincter controls the movement of food from the esophagus to the stomach.

Histology of the Esophagus

The mucosa of the esophagus is made up of an epithelial lining that contains non-keratinized, stratified squamous epithelium, with a layer of basal and parabasal cells. This epithelium protects against erosion from food particles. The mucosa’s lamina propria contains mucus-secreting glands. The muscularis layer changes according to location: In the upper third of the esophagus, the muscularis is skeletal muscle. In the middle third, it is both skeletal and smooth muscle. In the lower third, it is smooth muscle. As mentioned previously, the most superficial layer of the esophagus is called the adventitia, not the serosa. In contrast to the stomach and intestines, the loose connective tissue of the adventitia is not covered by a fold of visceral peritoneum. The digestive functions of the esophagus are identified in [\[link\]](#).

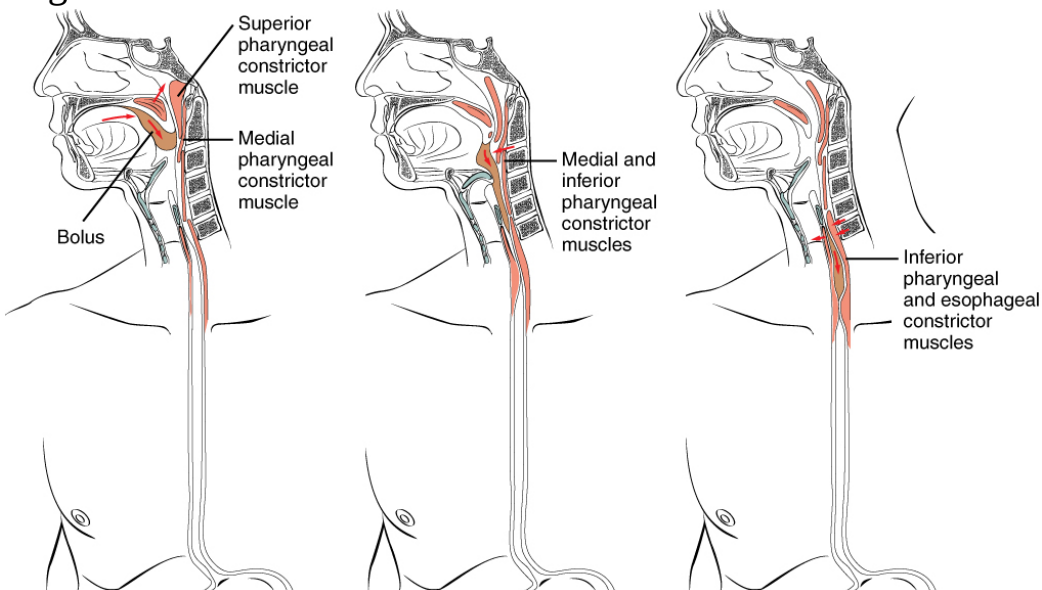
| Digestive Functions of the Esophagus | |
|---------------------------------------|---|
| Action | Outcome |
| Upper esophageal sphincter relaxation | Allows the bolus to move from the laryngopharynx to the esophagus |
| Peristalsis | Propels the bolus through the esophagus |
| Lower esophageal sphincter relaxation | Allows the bolus to move from the esophagus into the stomach and prevents chime from entering the esophagus |

| Digestive Functions of the Esophagus | |
|--------------------------------------|--|
| Action | Outcome |
| Mucus secretion | Lubricates the esophagus, allowing easy passage of the bolus |

Deglutition

Deglutition is another word for swallowing—the movement of food from the mouth to the stomach. The entire process takes about 4 to 8 seconds for solid or semisolid food, and about 1 second for very soft food and liquids. Although this sounds quick and effortless, deglutition is, in fact, a complex process that involves both the skeletal muscle of the tongue and the muscles of the pharynx and esophagus. It is aided by the presence of mucus and saliva. There are three stages in deglutition: the voluntary phase, the pharyngeal phase, and the esophageal phase ([\[link\]](#)). The autonomic nervous system controls the latter two phases.

Deglutition



Deglutition includes the voluntary phase and two involuntary phases: the pharyngeal phase and the esophageal phase.

The Voluntary Phase

The **voluntary phase** of deglutition (also known as the oral or buccal phase) is so called because you can control when you swallow food. In this phase, chewing has been completed and swallowing is set in motion. The tongue moves upward and backward against the palate, pushing the bolus to the back of the oral cavity and into the oropharynx. Other muscles keep the mouth closed and prevent food from falling out. At this point, the two involuntary phases of swallowing begin.

The Pharyngeal Phase

In the pharyngeal phase, stimulation of receptors in the oropharynx sends impulses to the deglutition center (a collection of neurons that controls swallowing) in the medulla oblongata. Impulses are then sent back to the uvula and soft palate, causing them to move upward and close off the nasopharynx. The laryngeal muscles also constrict to prevent aspiration of food into the trachea. At this point, deglutition apnea takes place, which means that breathing ceases for a very brief time. Contractions of the pharyngeal constrictor muscles move the bolus through the oropharynx and laryngopharynx. Relaxation of the upper esophageal sphincter then allows food to enter the esophagus.

The Esophageal Phase

The entry of food into the esophagus marks the beginning of the esophageal phase of deglutition and the initiation of peristalsis. As in the previous phase, the complex neuromuscular actions are controlled by the medulla oblongata. Peristalsis propels the bolus through the esophagus and toward the stomach. The circular muscle layer of the muscularis contracts, pinching

the esophageal wall and forcing the bolus forward. At the same time, the longitudinal muscle layer of the muscularis also contracts, shortening this area and pushing out its walls to receive the bolus. In this way, a series of contractions keeps moving food toward the stomach. When the bolus nears the stomach, distention of the esophagus initiates a short reflex relaxation of the lower esophageal sphincter that allows the bolus to pass into the stomach. During the esophageal phase, esophageal glands secrete mucus that lubricates the bolus and minimizes friction.

Note:



Watch this [animation](#) to see how swallowing is a complex process that involves the nervous system to coordinate the actions of upper respiratory and digestive activities. During which stage of swallowing is there a risk of food entering respiratory pathways and how is this risk blocked?

Chapter Review

In the mouth, the tongue and the teeth begin mechanical digestion, and saliva begins chemical digestion. The pharynx, which plays roles in breathing and vocalization as well as digestion, runs from the nasal and oral cavities superiorly to the esophagus inferiorly (for digestion) and to the larynx anteriorly (for respiration). During deglutition (swallowing), the soft palate rises to close off the nasopharynx, the larynx elevates, and the epiglottis folds over the glottis. The esophagus includes an upper esophageal sphincter made of skeletal muscle, which regulates the movement of food from the pharynx to the esophagus. It also has a lower esophageal sphincter, made of smooth muscle, which controls the passage

of food from the esophagus to the stomach. Cells in the esophageal wall secrete mucus that eases the passage of the food bolus.

Interactive Link Questions

Exercise:

Problem:

Watch this [animation](#) to see how swallowing is a complex process that involves the nervous system to coordinate the actions of upper respiratory and digestive activities. During which stage of swallowing is there a risk of food entering respiratory pathways and how is this risk blocked?

Solution:

Answers may vary.

Review Questions

Exercise:

Problem:

Which of these ingredients in saliva is responsible for activating salivary amylase?

- a. mucus
- b. phosphate ions
- c. chloride ions
- d. urea

Solution:

C

Exercise:

Problem: Which of these statements about the pharynx is true?

- a. It extends from the nasal and oral cavities superiorly to the esophagus anteriorly.
- b. The oropharynx is continuous superiorly with the nasopharynx.
- c. The nasopharynx is involved in digestion.
- d. The laryngopharynx is composed partially of cartilage.

Solution:

B

Exercise:

Problem:

Which structure is located where the esophagus penetrates the diaphragm?

- a. esophageal hiatus
- b. cardiac orifice
- c. upper esophageal sphincter
- d. lower esophageal sphincter

Solution:

A

Exercise:

Problem:

Which phase of deglutition involves contraction of the longitudinal muscle layer of the muscularis?

- a. voluntary phase

- b. buccal phase
- c. pharyngeal phase
- d. esophageal phase

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

The composition of saliva varies from gland to gland. Discuss how saliva produced by the parotid gland differs in action from saliva produced by the sublingual gland.

Solution:

Parotid gland saliva is watery with little mucus but a lot of amylase, which allows it to mix freely with food during mastication and begin the digestion of carbohydrates. In contrast, sublingual gland saliva has a lot of mucus with the least amount of amylase of all the salivary glands. The high mucus content serves to lubricate the food for swallowing.

Exercise:

Problem:

During a hockey game, the puck hits a player in the mouth, knocking out all eight of his most anterior teeth. Which teeth did the player lose and how does this loss affect food ingestion?

Solution:

The incisors. Since these teeth are used for tearing off pieces of food during ingestion, the player will need to ingest foods that have already been cut into bite-sized pieces until the broken teeth are replaced.

Exercise:

Problem:What prevents swallowed food from entering the airways?

Solution:

Usually when food is swallowed, involuntary muscle contractions cause the soft palate to rise and close off the nasopharynx. The larynx also is pulled up, and the epiglottis folds over the glottis. These actions block off the air passages.

Exercise:

Problem:

Explain the mechanism responsible for gastroesophageal reflux.

Solution:

If the lower esophageal sphincter does not close completely, the stomach's acidic contents can back up into the esophagus, a phenomenon known as GERD.

Exercise:

Problem:

Describe the three processes involved in the esophageal phase of deglutition.

Solution:

Peristalsis moves the bolus down the esophagus and toward the stomach. Esophageal glands secrete mucus that lubricates the bolus and reduces friction. When the bolus nears the stomach, the lower

esophageal sphincter relaxes, allowing the bolus to pass into the stomach.

References

van Loon FPL, Holmes SJ, Sirotkin B, Williams W, Cochi S, Hadler S, Lindegren ML. Morbidity and Mortality Weekly Report: Mumps surveillance -- United States, 1988–1993 [Internet]. Atlanta, GA: Center for Disease Control; [cited 2013 Apr 3]. Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/00038546.htm>.

Glossary

bolus

mass of chewed food

cementum

bone-like tissue covering the root of a tooth

crown

portion of tooth visible superior to the gum line

cuspid

(also, canine) pointed tooth used for tearing and shredding food

deciduous tooth

one of 20 “baby teeth”

deglutition

three-stage process of swallowing

dens

tooth

dentin

bone-like tissue immediately deep to the enamel of the crown or cementum of the root of a tooth

dentition

set of teeth

enamel

covering of the dentin of the crown of a tooth

esophagus

muscular tube that runs from the pharynx to the stomach

fauces

opening between the oral cavity and the oropharynx

gingiva

gum

incisor

midline, chisel-shaped tooth used for cutting into food

labium

lip

labial frenulum

midline mucous membrane fold that attaches the inner surface of the lips to the gums

laryngopharynx

part of the pharynx that functions in respiration and digestion

lingual frenulum

mucous membrane fold that attaches the bottom of the tongue to the floor of the mouth

lingual lipase

digestive enzyme from glands in the tongue that acts on triglycerides

lower esophageal sphincter

smooth muscle sphincter that regulates food movement from the esophagus to the stomach

molar

tooth used for crushing and grinding food

oral cavity

(also, buccal cavity) mouth

oral vestibule

part of the mouth bounded externally by the cheeks and lips, and internally by the gums and teeth

oropharynx

part of the pharynx continuous with the oral cavity that functions in respiration and digestion

palatoglossal arch

muscular fold that extends from the lateral side of the soft palate to the base of the tongue

palatopharyngeal arch

muscular fold that extends from the lateral side of the soft palate to the side of the pharynx

parotid gland

one of a pair of major salivary glands located inferior and anterior to the ears

permanent tooth

one of 32 adult teeth

pharynx

throat

premolar

(also, bicuspid) transitional tooth used for mastication, crushing, and grinding food

pulp cavity

deepest portion of a tooth, containing nerve endings and blood vessels

root

portion of a tooth embedded in the alveolar processes beneath the gum line

saliva

aqueous solution of proteins and ions secreted into the mouth by the salivary glands

salivary amylase

digestive enzyme in saliva that acts on starch

salivary gland

an exocrine gland that secretes a digestive fluid called saliva

salivation

secretion of saliva

soft palate

posterior region of the bottom portion of the nasal cavity that consists of skeletal muscle

sublingual gland

one of a pair of major salivary glands located beneath the tongue

submandibular gland

one of a pair of major salivary glands located in the floor of the mouth

tongue

accessory digestive organ of the mouth, the bulk of which is composed of skeletal muscle

upper esophageal sphincter

skeletal muscle sphincter that regulates food movement from the pharynx to the esophagus

voluntary phase

initial phase of deglutition, in which the bolus moves from the mouth to the oropharynx

The Stomach

By the end of this section, you will be able to:

- Label on a diagram the four main regions of the stomach, its curvatures, and its sphincter
- Identify the four main types of secreting cells in gastric glands, and their important products
- Explain why the stomach does not digest itself
- Describe the mechanical and chemical digestion of food entering the stomach

Although a minimal amount of carbohydrate digestion occurs in the mouth, chemical digestion really gets underway in the stomach. An expansion of the alimentary canal that lies immediately inferior to the esophagus, the stomach links the esophagus to the first part of the small intestine (the duodenum) and is relatively fixed in place at its esophageal and duodenal ends. In between, however, it can be a highly active structure, contracting and continually changing position and size. These contractions provide mechanical assistance to digestion. The empty stomach is only about the size of your fist, but can stretch to hold as much as 4 liters of food and fluid, or more than 75 times its empty volume, and then return to its resting size when empty. Although you might think that the size of a person's stomach is related to how much food that individual consumes, body weight does not correlate with stomach size. Rather, when you eat greater quantities of food—such as at holiday dinner—you stretch the stomach more than when you eat less.

Popular culture tends to refer to the stomach as the location where all digestion takes place. Of course, this is not true. An important function of the stomach is to serve as a temporary holding chamber. You can ingest a meal far more quickly than it can be digested and absorbed by the small intestine. Thus, the stomach holds food and parses only small amounts into the small intestine at a time. Foods are not processed in the order they are eaten; rather, they are mixed together with digestive juices in the stomach until they are converted into chyme, which is released into the small intestine.

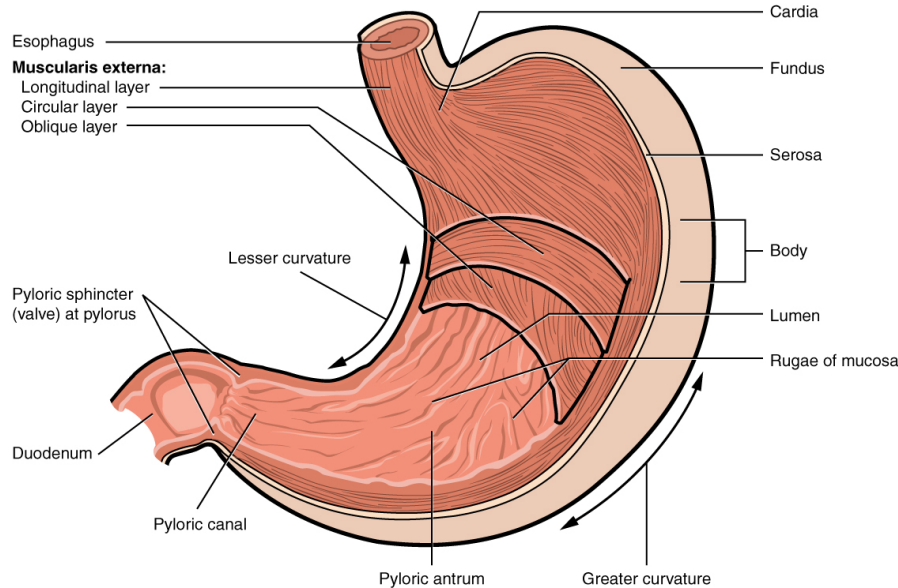
As you will see in the sections that follow, the stomach plays several important roles in chemical digestion, including the continued digestion of carbohydrates and the initial digestion of proteins and triglycerides. Little if any nutrient absorption occurs in the stomach, with the exception of the negligible amount of nutrients in alcohol.

Structure

There are four main regions in the **stomach**: the cardia, fundus, body, and pylorus ([\[link\]](#)). The **cardia** (or cardiac region) is the point where the esophagus connects to the stomach and through which food passes into the stomach. Located inferior to the diaphragm, above and to the left of the cardia, is the dome-shaped **fundus**. Below the fundus is the **body**, the main part of the stomach. The funnel-shaped **pylorus** connects the stomach to the duodenum. The wider end of the funnel, the **pyloric antrum**, connects

to the body of the stomach. The narrower end is called the **pyloric canal**, which connects to the duodenum. The smooth muscle **pyloric sphincter** is located at this latter point of connection and controls stomach emptying. In the absence of food, the stomach deflates inward, and its mucosa and submucosa fall into a large fold called a **ruga**.

Stomach



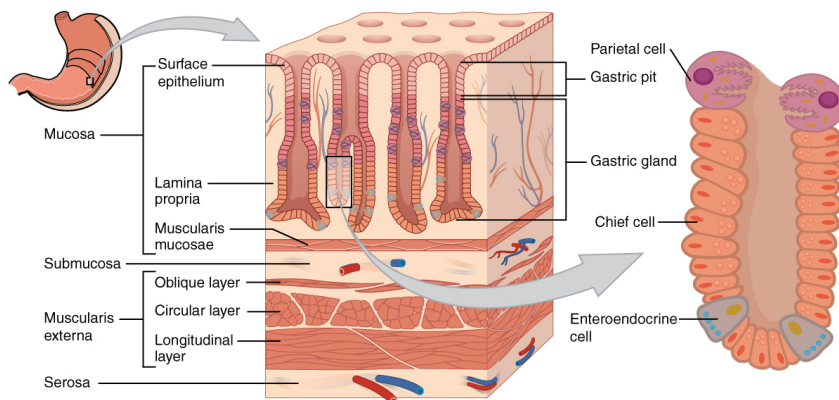
The stomach has four major regions: the cardia, fundus, body, and pylorus. The addition of an inner oblique smooth muscle layer gives the muscularis the ability to vigorously churn and mix food.

The convex lateral surface of the stomach is called the greater curvature; the concave medial border is the lesser curvature. The stomach is held in place by the lesser omentum, which extends from the liver to the lesser curvature, and the greater omentum, which runs from the greater curvature to the posterior abdominal wall.

Histology

The wall of the stomach is made of the same four layers as most of the rest of the alimentary canal, but with adaptations to the mucosa and muscularis for the unique functions of this organ. In addition to the typical circular and longitudinal smooth muscle layers, the muscularis has an inner oblique smooth muscle layer ([\[link\]](#)). As a result, in addition to moving food through the canal, the stomach can vigorously churn food, mechanically breaking it down into smaller particles.

Histology of the Stomach



The stomach wall is adapted for the functions of the stomach. In the epithelium, gastric pits lead to gastric glands that secrete gastric juice. The gastric glands (one gland is shown enlarged on the right) contain different types of cells that secrete a variety of enzymes, including hydrochloride acid, which activates the protein-digesting enzyme pepsin.

The stomach mucosa's epithelial lining consists only of surface mucus cells, which secrete a protective coat of alkaline mucus. A vast number of **gastric pits** dot the surface of the epithelium, giving it the appearance of a well-used pincushion, and mark the entry to each **gastric gland**, which secretes a complex digestive fluid referred to as gastric juice.

Although the walls of the gastric pits are made up primarily of mucus cells, the gastric glands are made up of different types of cells. The glands of the cardia and pylorus are composed primarily of mucus-secreting cells. Cells that make up the pyloric antrum secrete mucus and a number of hormones, including the majority of the stimulatory hormone, **gastrin**. The much larger glands of the fundus and body of the stomach, the site of most chemical digestion, produce most of the gastric secretions. These glands are made up of a variety of secretory cells. These include parietal cells, chief cells, mucous neck cells, and enteroendocrine cells.

Parietal cells—Located primarily in the middle region of the gastric glands are **parietal cells**, which are among the most highly differentiated of the body's epithelial cells. These relatively large cells produce both **hydrochloric acid (HCl)** and **intrinsic factor**. HCl is responsible for the high acidity (pH 1.5 to 3.5) of the stomach contents and is needed to activate the protein-digesting enzyme, pepsin. The acidity also kills much of the bacteria you ingest with food and helps to denature proteins, making them more available for enzymatic digestion. Intrinsic factor is a glycoprotein necessary for the absorption of vitamin B₁₂ in the small intestine.

Chief cells—Located primarily in the basal regions of gastric glands are **chief cells**, which secrete **pepsinogen**, the inactive proenzyme form of pepsin. HCl is necessary for the conversion of pepsinogen to pepsin.

Mucous neck cells—Gastric glands in the upper part of the stomach contain **mucous neck cells** that secrete thin, acidic mucus that is much different from the mucus secreted by the goblet cells of the surface epithelium. The role of this mucus is not currently known.

Enteroendocrine cells—Finally, **enteroendocrine cells** found in the gastric glands secrete various hormones into the interstitial fluid of the lamina propria. These include gastrin, which is released mainly by enteroendocrine **G cells**.

[\[link\]](#) describes the digestive functions of important hormones secreted by the stomach.

Note:



Watch this [animation](#) that depicts the structure of the stomach and how this structure functions in the initiation of protein digestion. This view of the stomach shows the characteristic rugae. What is the function of these rugae?

| Hormones Secreted by the Stomach | | | | |
|----------------------------------|-----------------|---------------------|--------------|--------|
| Hormone | Production site | Production stimulus | Target organ | Action |

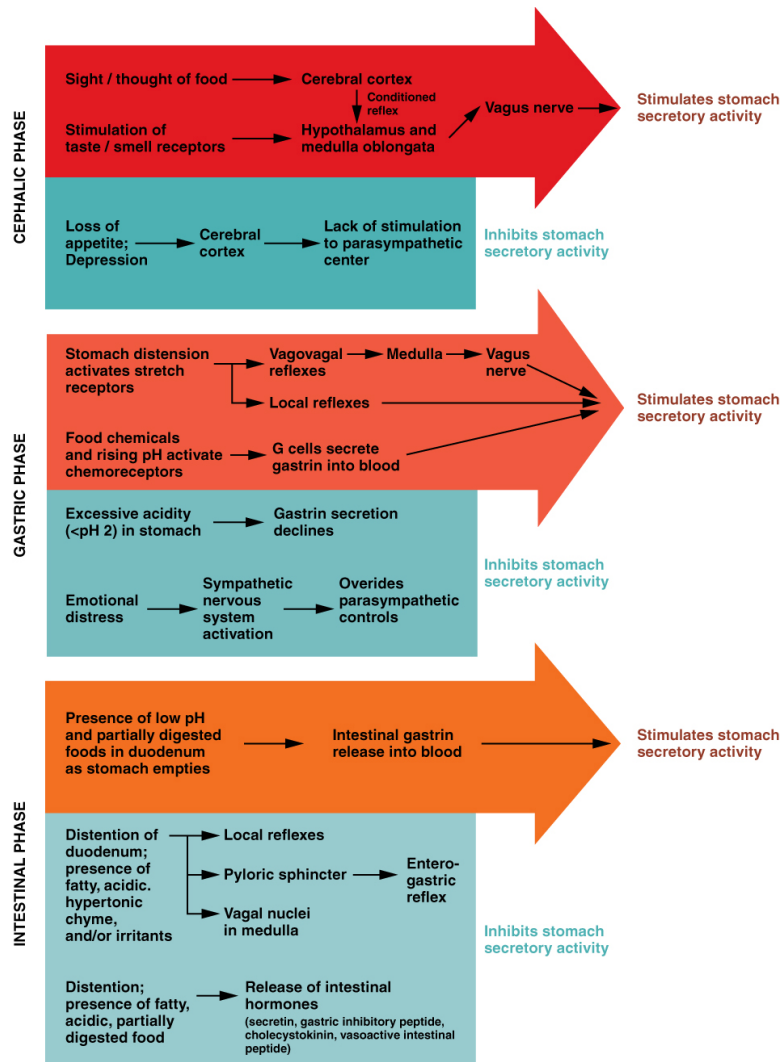
| Hormones Secreted by the Stomach | | | | |
|---|--|---|---------------------|--|
| Hormone | Production site | Production stimulus | Target organ | Action |
| Gastrin | Stomach mucosa, mainly G cells of the pyloric antrum | Presence of peptides and amino acids in stomach | Stomach | Increases secretion by gastric glands; promotes gastric emptying |
| Gastrin | Stomach mucosa, mainly G cells of the pyloric antrum | Presence of peptides and amino acids in stomach | Small intestine | Promotes intestinal muscle contraction |
| Gastrin | Stomach mucosa, mainly G cells of the pyloric antrum | Presence of peptides and amino acids in stomach | Ileocecal valve | Relaxes valve |
| Gastrin | Stomach mucosa, mainly G cells of the pyloric antrum | Presence of peptides and amino acids in stomach | Large intestine | Triggers mass movements |
| Ghrelin | Stomach mucosa, mainly fundus | Fasting state (levels increase just prior to meals) | Hypothalamus | Regulates food intake, primarily by stimulating hunger and satiety |

| Hormones Secreted by the Stomach | | | | |
|---|---|---|---------------------|--|
| Hormone | Production site | Production stimulus | Target organ | Action |
| Histamine | Stomach mucosa | Presence of food in the stomach | Stomach | Stimulates parietal cells to release HCl |
| Serotonin | Stomach mucosa | Presence of food in the stomach | Stomach | Contracts stomach muscle |
| Somatostatin | Mucosa of stomach, especially pyloric antrum; also duodenum | Presence of food in the stomach; sympathetic axon stimulation | Stomach | Restricts all gastric secretions, gastric motility, and emptying |
| Somatostatin | Mucosa of stomach, especially pyloric antrum; also duodenum | Presence of food in the stomach; sympathetic axon stimulation | Pancreas | Restricts pancreatic secretions |
| Somatostatin | Mucosa of stomach, especially pyloric antrum; also duodenum | Presence of food in the stomach; sympathetic axon stimulation | Small intestine | Reduces intestinal absorption by reducing blood flow |

Gastric Secretion

The secretion of gastric juice is controlled by both nerves and hormones. Stimuli in the brain, stomach, and small intestine activate or inhibit gastric juice production. This is why the three phases of gastric secretion are called the cephalic, gastric, and intestinal phases ([link](#)). However, once gastric secretion begins, all three phases can occur simultaneously.

The Three Phases of Gastric Secretion



Gastric secretion occurs in three phases: cephalic, gastric, and intestinal. During each phase, the secretion of gastric juice can be stimulated or inhibited.

The **cephalic phase** (reflex phase) of gastric secretion, which is relatively brief, takes place before food enters the stomach. The smell, taste, sight, or thought of food triggers

this phase. For example, when you bring a piece of sushi to your lips, impulses from receptors in your taste buds or the nose are relayed to your brain, which returns signals that increase gastric secretion to prepare your stomach for digestion. This enhanced secretion is a conditioned reflex, meaning it occurs only if you like or want a particular food. Depression and loss of appetite can suppress the cephalic reflex.

The **gastric phase** of secretion lasts 3 to 4 hours, and is set in motion by local neural and hormonal mechanisms triggered by the entry of food into the stomach. For example, when your sushi reaches the stomach, it creates distention that activates the stretch receptors. This stimulates parasympathetic neurons to release acetylcholine, which then provokes increased secretion of gastric juice. Partially digested proteins, caffeine, and rising pH stimulate the release of gastrin from enteroendocrine G cells, which in turn induces parietal cells to increase their production of HCl, which is needed to create an acidic environment for the conversion of pepsinogen to pepsin, and protein digestion. Additionally, the release of gastrin activates vigorous smooth muscle contractions. However, it should be noted that the stomach does have a natural means of avoiding excessive acid secretion and potential heartburn. Whenever pH levels drop too low, cells in the stomach react by suspending HCl secretion and increasing mucous secretions.

The **intestinal phase** of gastric secretion has both excitatory and inhibitory elements. The duodenum has a major role in regulating the stomach and its emptying. When partially digested food fills the duodenum, intestinal mucosal cells release a hormone called intestinal (enteric) gastrin, which further excites gastric juice secretion. This stimulatory activity is brief, however, because when the intestine distends with chyme, the enterogastric reflex inhibits secretion. One of the effects of this reflex is to close the pyloric sphincter, which blocks additional chyme from entering the duodenum.

The Mucosal Barrier

The mucosa of the stomach is exposed to the highly corrosive acidity of gastric juice. Gastric enzymes that can digest protein can also digest the stomach itself. The stomach is protected from self-digestion by the **mucosal barrier**. This barrier has several components. First, the stomach wall is covered by a thick coating of bicarbonate-rich mucus. This mucus forms a physical barrier, and its bicarbonate ions neutralize acid. Second, the epithelial cells of the stomach's mucosa meet at tight junctions, which block gastric juice from penetrating the underlying tissue layers. Finally, stem cells located where gastric glands join the gastric pits quickly replace damaged epithelial mucosal cells, when the epithelial cells are shed. In fact, the surface epithelium of the stomach is completely replaced every 3 to 6 days.

Note:

Homeostatic Imbalances

Ulcers: When the Mucosal Barrier Breaks Down

As effective as the mucosal barrier is, it is not a “fail-safe” mechanism. Sometimes, gastric juice eats away at the superficial lining of the stomach mucosa, creating erosions, which mostly heal on their own. Deeper and larger erosions are called ulcers.

Why does the mucosal barrier break down? A number of factors can interfere with its ability to protect the stomach lining. The majority of all ulcers are caused by either excessive intake of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, or *Helicobacter pylori* infection.

Antacids help relieve symptoms of ulcers such as “burning” pain and indigestion. When ulcers are caused by NSAID use, switching to other classes of pain relievers allows healing. When caused by *H. pylori* infection, antibiotics are effective.

A potential complication of ulcers is perforation: Perforated ulcers create a hole in the stomach wall, resulting in peritonitis (inflammation of the peritoneum). These ulcers must be repaired surgically.

Digestive Functions of the Stomach

The stomach participates in virtually all the digestive activities with the exception of ingestion and defecation. Although almost all absorption takes place in the small intestine, the stomach does absorb some nonpolar substances, such as alcohol and aspirin.

Mechanical Digestion

Within a few moments after food enters your stomach, mixing waves begin to occur at intervals of approximately 20 seconds. A **mixing wave** is a unique type of peristalsis that mixes and softens the food with gastric juices to create chyme. The initial mixing waves are relatively gentle, but these are followed by more intense waves, starting at the body of the stomach and increasing in force as they reach the pylorus. It is fair to say that long before your sushi exits through the pyloric sphincter, it bears little resemblance to the sushi you ate.

The pylorus, which holds around 30 mL (1 fluid ounce) of chyme, acts as a filter, permitting only liquids and small food particles to pass through the mostly, but not fully, closed pyloric sphincter. In a process called **gastric emptying**, rhythmic mixing waves force about 3 mL of chyme at a time through the pyloric sphincter and into the duodenum. Release of a greater amount of chyme at one time would overwhelm the capacity of the small intestine to handle it. The rest of the chyme is pushed back into the body of the stomach, where it continues mixing. This process is repeated when the next mixing waves force more chyme into the duodenum.

Gastric emptying is regulated by both the stomach and the duodenum. The presence of chyme in the duodenum activates receptors that inhibit gastric secretion. This prevents additional chyme from being released by the stomach before the duodenum is ready to process it.

Chemical Digestion

The fundus plays an important role, because it stores both undigested food and gases that are released during the process of chemical digestion. Food may sit in the fundus of the stomach for a while before being mixed with the chyme. While the food is in the fundus, the digestive activities of salivary amylase continue until the food begins mixing with the acidic chyme. Ultimately, mixing waves incorporate this food with the chyme, the acidity of which inactivates salivary amylase and activates lingual lipase. Lingual lipase then begins breaking down triglycerides into free fatty acids, and mono- and diglycerides.

The breakdown of protein begins in the stomach through the actions of HCl and the enzyme pepsin. During infancy, gastric glands also produce rennin, an enzyme that helps digest milk protein.

Its numerous digestive functions notwithstanding, there is only one stomach function necessary to life: the production of intrinsic factor. The intestinal absorption of vitamin B₁₂, which is necessary for both the production of mature red blood cells and normal neurological functioning, cannot occur without intrinsic factor. People who undergo total gastrectomy (stomach removal)—for life-threatening stomach cancer, for example—can survive with minimal digestive dysfunction if they receive vitamin B₁₂ injections.

The contents of the stomach are completely emptied into the duodenum within 2 to 4 hours after you eat a meal. Different types of food take different amounts of time to process. Foods heavy in carbohydrates empty fastest, followed by high-protein foods. Meals with a high triglyceride content remain in the stomach the longest. Since enzymes in the small intestine digest fats slowly, food can stay in the stomach for 6 hours or longer when the duodenum is processing fatty chyme. However, note that this is still a fraction of the 24 to 72 hours that full digestion typically takes from start to finish.

Chapter Review

The stomach participates in all digestive activities except ingestion and defecation. It vigorously churns food. It secretes gastric juices that break down food and absorb certain drugs, including aspirin and some alcohol. The stomach begins the digestion of protein and continues the digestion of carbohydrates and fats. It stores food as an acidic liquid called chyme, and releases it gradually into the small intestine through the pyloric sphincter.

Interactive Link Questions

Exercise:

Problem:

Watch this [animation](#) that depicts the structure of the stomach and how this structure functions in the initiation of protein digestion. This view of the stomach shows the characteristic rugae. What is the function of these rugae?

Solution:

Answers may vary.

Review Questions

Exercise:

Problem: Which of these cells secrete hormones?

- a. parietal cells
 - b. mucous neck cells
 - c. enteroendocrine cells
 - d. chief cells
-

Solution:

C

Exercise:

Problem: Where does the majority of chemical digestion in the stomach occur?

- a. fundus and body
 - b. cardia and fundus
 - c. body and pylorus
 - d. body
-

Solution:

A

Exercise:

Problem:

During gastric emptying, chyme is released into the duodenum through the _____.

- a. esophageal hiatus
- b. pyloric antrum
- c. pyloric canal
- d. pyloric sphincter

Solution:

D

Exercise:

Problem: Parietal cells secrete _____.

- a. gastrin
- b. hydrochloric acid
- c. pepsin
- d. pepsinogen

Solution:

B

Critical Thinking Questions**Exercise:****Problem:**

Explain how the stomach is protected from self-digestion and why this is necessary.

Solution:

The mucosal barrier protects the stomach from self-digestion. It includes a thick coating of bicarbonate-rich mucus; the mucus is physically protective, and bicarbonate neutralizes gastric acid. Epithelial cells meet at tight junctions, which block gastric juice from penetrating the underlying tissue layers, and stem cells quickly replace sloughed off epithelial mucosal cells.

Exercise:**Problem:**

Describe unique anatomical features that enable the stomach to perform digestive functions.

Solution:

The stomach has an additional inner oblique smooth muscle layer that helps the muscularis churn and mix food. The epithelium includes gastric glands that secrete gastric fluid. The gastric fluid consists mainly of mucous, HCl, and the enzyme pepsin released as pepsinogen.

Glossary**body**

mid-portion of the stomach

cardia

(also, cardiac region) part of the stomach surrounding the cardiac orifice (esophageal hiatus)

cephalic phase

(also, reflex phase) initial phase of gastric secretion that occurs before food enters the stomach

chief cell

gastric gland cell that secretes pepsinogen

enteroendocrine cell

gastric gland cell that releases hormones

fundus

dome-shaped region of the stomach above and to the left of the cardia

G cell

gastrin-secreting enteroendocrine cell

gastric emptying

process by which mixing waves gradually cause the release of chyme into the duodenum

gastric gland

gland in the stomach mucosal epithelium that produces gastric juice

gastric phase

phase of gastric secretion that begins when food enters the stomach

gastric pit

narrow channel formed by the epithelial lining of the stomach mucosa

gastrin

peptide hormone that stimulates secretion of hydrochloric acid and gut motility

hydrochloric acid (HCl)

digestive acid secreted by parietal cells in the stomach

intrinsic factor

glycoprotein required for vitamin B₁₂ absorption in the small intestine

intestinal phase

phase of gastric secretion that begins when chyme enters the intestine

mixing wave

unique type of peristalsis that occurs in the stomach

mucosal barrier

protective barrier that prevents gastric juice from destroying the stomach itself

mucous neck cell

gastric gland cell that secretes a uniquely acidic mucus

parietal cell

gastric gland cell that secretes hydrochloric acid and intrinsic factor

pepsinogen

inactive form of pepsin

pyloric antrum

wider, more superior part of the pylorus

pyloric canal

narrow, more inferior part of the pylorus

pyloric sphincter

sphincter that controls stomach emptying

pylorus

lower, funnel-shaped part of the stomach that is continuous with the duodenum

ruga

fold of alimentary canal mucosa and submucosa in the empty stomach and other organs

stomach

alimentary canal organ that contributes to chemical and mechanical digestion of food from the esophagus before releasing it, as chyme, to the small intestine

The Small and Large Intestines

By the end of this section, you will be able to:

- Compare and contrast the location and gross anatomy of the small and large intestines
- Identify three main adaptations of the small intestine wall that increase its absorptive capacity
- Describe the mechanical and chemical digestion of chyme upon its release into the small intestine
- List three features unique to the wall of the large intestine and identify their contributions to its function
- Identify the beneficial roles of the bacterial flora in digestive system functioning
- Trace the pathway of food waste from its point of entry into the large intestine through its exit from the body as feces

The word intestine is derived from a Latin root meaning “internal,” and indeed, the two organs together nearly fill the interior of the abdominal cavity. In addition, called the small and large bowel, or colloquially the “guts,” they constitute the greatest mass and length of the alimentary canal and, with the exception of ingestion, perform all digestive system functions.

The Small Intestine

Chyme released from the stomach enters the **small intestine**, which is the primary digestive organ in the body. Not only is this where most digestion occurs, it is also where practically all absorption occurs. The longest part of the alimentary canal, the small intestine is about 3.05 meters (10 feet) long in a living person (but about twice as long in a cadaver due to the loss of muscle tone). Since this makes it about five times longer than the large intestine, you might wonder why it is called “small.” In fact, its name derives from its relatively smaller diameter of only about 2.54 cm (1 in), compared with 7.62 cm (3 in) for the large intestine. As we’ll see shortly, in addition to its length, the folds and projections of the lining of the small intestine work to give it an enormous surface area, which is approximately 200 m², more than 100 times the surface area of your skin. This large

surface area is necessary for complex processes of digestion and absorption that occur within it.

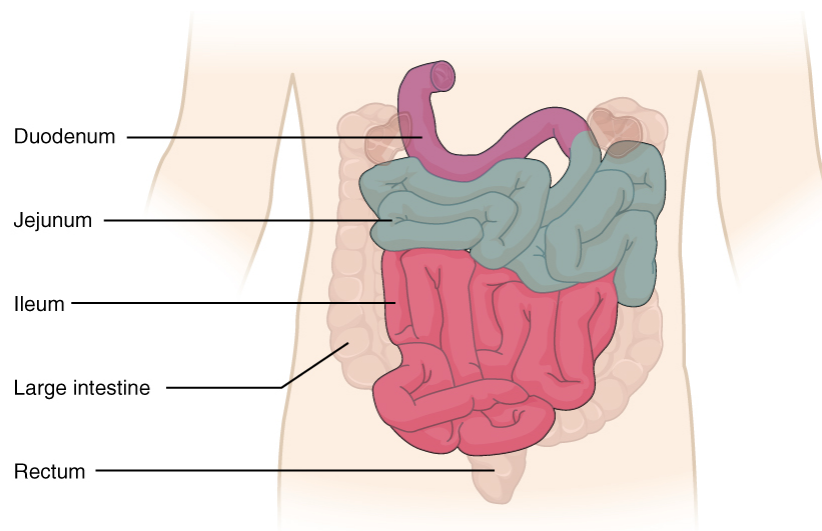
Structure

The coiled tube of the small intestine is subdivided into three regions. From proximal (at the stomach) to distal, these are the duodenum, jejunum, and ileum ([\[link\]](#)).

The shortest region is the 25.4-cm (10-in) **duodenum**, which begins at the pyloric sphincter. Just past the pyloric sphincter, it bends posteriorly behind the peritoneum, becoming retroperitoneal, and then makes a C-shaped curve around the head of the pancreas before ascending anteriorly again to return to the peritoneal cavity and join the jejunum. The duodenum can therefore be subdivided into four segments: the superior, descending, horizontal, and ascending duodenum.

Of particular interest is the **hepatopancreatic ampulla** (ampulla of Vater). Located in the duodenal wall, the ampulla marks the transition from the anterior portion of the alimentary canal to the mid-region, and is where the bile duct (through which bile passes from the liver) and the **main pancreatic duct** (through which pancreatic juice passes from the pancreas) join. This ampulla opens into the duodenum at a tiny volcano-shaped structure called the **major duodenal papilla**. The **hepatopancreatic sphincter** (sphincter of Oddi) regulates the flow of both bile and pancreatic juice from the ampulla into the duodenum.

Small Intestine



The three regions of the small intestine are the duodenum, jejunum, and ileum.

The **jejunum** is about 0.9 meters (3 feet) long (in life) and runs from the duodenum to the ileum. Jejunum means “empty” in Latin and supposedly was so named by the ancient Greeks who noticed it was always empty at death. No clear demarcation exists between the jejunum and the final segment of the small intestine, the ileum.

The **ileum** is the longest part of the small intestine, measuring about 1.8 meters (6 feet) in length. It is thicker, more vascular, and has more developed mucosal folds than the jejunum. The ileum joins the cecum, the first portion of the large intestine, at the **ileocecal sphincter** (or valve). The jejunum and ileum are tethered to the posterior abdominal wall by the mesentery. The large intestine frames these three parts of the small intestine.

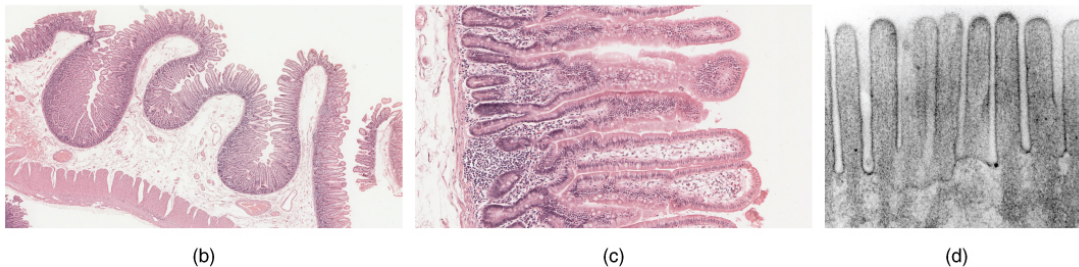
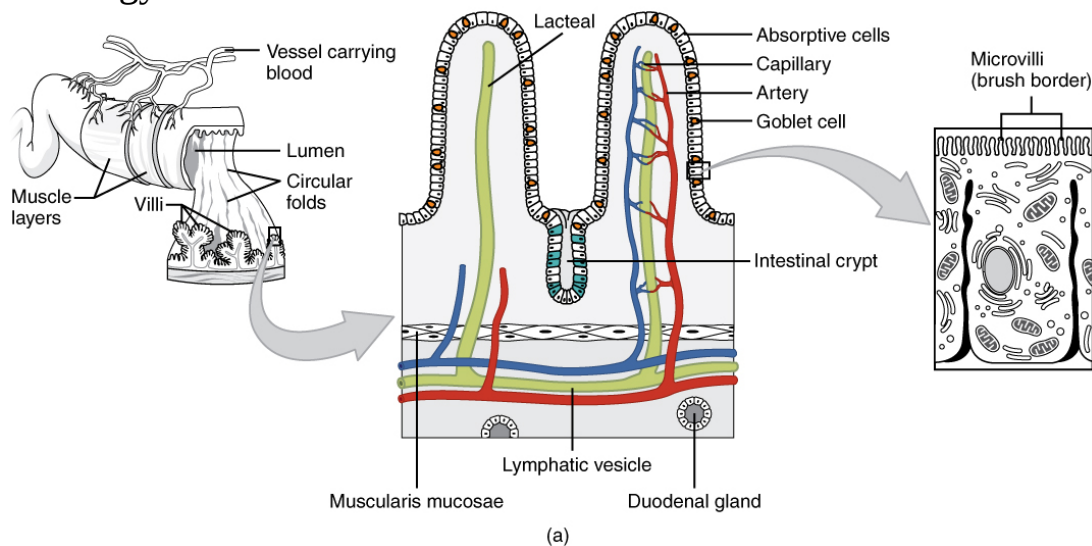
Parasympathetic nerve fibers from the vagus nerve and sympathetic nerve fibers from the thoracic splanchnic nerve provide extrinsic innervation to the small intestine. The superior mesenteric artery is its main arterial supply. Veins run parallel to the arteries and drain into the superior

mesenteric vein. Nutrient-rich blood from the small intestine is then carried to the liver via the hepatic portal vein.

Histology

The wall of the small intestine is composed of the same four layers typically present in the alimentary system. However, three features of the mucosa and submucosa are unique. These features, which increase the absorptive surface area of the small intestine more than 600-fold, include circular folds, villi, and microvilli ([\[link\]](#)). These adaptations are most abundant in the proximal two-thirds of the small intestine, where the majority of absorption occurs.

Histology of the Small Intestine



- (a) The absorptive surface of the small intestine is vastly enlarged by the presence of circular folds, villi, and microvilli.
(b) Micrograph of the circular folds. (c) Micrograph of the villi.

(d) Electron micrograph of the microvilli. From left to right, LM x 56, LM x 508, EM x 196,000. (credit b-d: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Circular folds

Also called a plica circulare, a **circular fold** is a deep ridge in the mucosa and submucosa. Beginning near the proximal part of the duodenum and ending near the middle of the ileum, these folds facilitate absorption. Their shape causes the chyme to spiral, rather than move in a straight line, through the small intestine. Spiraling slows the movement of chyme and provides the time needed for nutrients to be fully absorbed.

Villi

Within the circular folds are small (0.5–1 mm long) hairlike vascularized projections called **villi** (singular = villus) that give the mucosa a furry texture. There are about 20 to 40 villi per square millimeter, increasing the surface area of the epithelium tremendously. The mucosal epithelium, primarily composed of absorptive cells, covers the villi. In addition to muscle and connective tissue to support its structure, each villus contains a capillary bed composed of one arteriole and one venule, as well as a lymphatic capillary called a **lacteal**. The breakdown products of carbohydrates and proteins (sugars and amino acids) can enter the bloodstream directly, but lipid breakdown products are absorbed by the lacteals and transported to the bloodstream via the lymphatic system.

Microvilli

As their name suggests, **microvilli** (singular = microvillus) are much smaller ($1\ \mu\text{m}$) than villi. They are cylindrical apical surface extensions of the plasma membrane of the mucosa's epithelial cells, and are supported by microfilaments within those cells. Although their small size makes it difficult to see each microvillus, their combined microscopic appearance suggests a mass of bristles, which is termed the **brush border**. Fixed to the surface of the microvilli membranes are enzymes that finish digesting carbohydrates and proteins. There are an estimated 200 million microvilli per square millimeter of small intestine, greatly expanding the surface area of the plasma membrane and thus greatly enhancing absorption.

Intestinal Glands

In addition to the three specialized absorptive features just discussed, the mucosa between the villi is dotted with deep crevices that each lead into a tubular **intestinal gland** (crypt of Lieberkühn), which is formed by cells that line the crevices (see [\[link\]](#)). These produce **intestinal juice**, a slightly alkaline (pH 7.4 to 7.8) mixture of water and mucus. Each day, about 0.95 to 1.9 liters (1 to 2 quarts) are secreted in response to the distention of the small intestine or the irritating effects of chyme on the intestinal mucosa.

The submucosa of the duodenum is the only site of the complex mucus-secreting **duodenal glands** (Brunner's glands), which produce a bicarbonate-rich alkaline mucus that buffers the acidic chyme as it enters from the stomach.

The roles of the cells in the small intestinal mucosa are detailed in [\[link\]](#).

Cells of the Small Intestinal Mucosa

| Cells of the Small Intestinal Mucosa | | |
|---|-------------------------------|-----------------|
| Cell type | Location in the mucosa | Function |

| Cell type | Location in the mucosa | Function |
|------------------|-------------------------------|--|
| Absorptive | Epithelium/intestinal glands | Digestion and absorption of nutrients in chyme |
| Goblet | Epithelium/intestinal glands | Secretion of mucus |
| Paneth | Intestinal glands | Secretion of the bactericidal enzyme lysozyme; phagocytosis |
| G cells | Intestinal glands of duodenum | Secretion of the hormone intestinal gastrin |
| I cells | Intestinal glands of duodenum | Secretion of the hormone cholecystokinin, which stimulates release of pancreatic juices and bile |
| K cells | Intestinal glands | Secretion of the hormone glucose-dependent insulinotropic peptide, which stimulates the release of insulin |

Cells of the Small Intestinal Mucosa

| Cell type | Location in the mucosa | Function |
|-----------|---|--|
| M cells | Intestinal glands of duodenum and jejunum | Secretion of the hormone motilin, which accelerates gastric emptying, stimulates intestinal peristalsis, and stimulates the production of pepsin |
| S cells | Intestinal glands | Secretion of the hormone secretin |

Intestinal MALT

The lamina propria of the small intestine mucosa is studded with quite a bit of MALT. In addition to solitary lymphatic nodules, aggregations of intestinal MALT, which are typically referred to as Peyer's patches, are concentrated in the distal ileum, and serve to keep bacteria from entering the bloodstream. Peyer's patches are most prominent in young people and become less distinct as you age, which coincides with the general activity of our immune system.

Note:



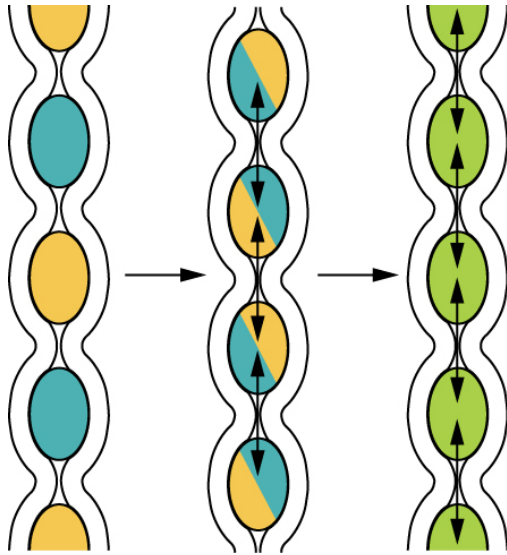
Watch this [animation](#) that depicts the structure of the small intestine, and, in particular, the villi. Epithelial cells continue the digestion and absorption of nutrients and transport these nutrients to the lymphatic and circulatory systems. In the small intestine, the products of food digestion are absorbed by different structures in the villi. Which structure absorbs and transports fats?

Mechanical Digestion in the Small Intestine

The movement of intestinal smooth muscles includes both segmentation and a form of peristalsis called migrating motility complexes. The kind of peristaltic mixing waves seen in the stomach are not observed here.

If you could see into the small intestine when it was going through segmentation, it would look as if the contents were being shoved incrementally back and forth, as the rings of smooth muscle repeatedly contract and then relax. Segmentation in the small intestine does not force chyme through the tract. Instead, it combines the chyme with digestive juices and pushes food particles against the mucosa to be absorbed. The duodenum is where the most rapid segmentation occurs, at a rate of about 12 times per minute. In the ileum, segmentations are only about eight times per minute ([link](#)).

Segmentation



Segmentation separates chyme and then pushes it back together, mixing it and providing time for digestion and absorption.

When most of the chyme has been absorbed, the small intestinal wall becomes less distended. At this point, the localized segmentation process is replaced by transport movements. The duodenal mucosa secretes the hormone **motilin**, which initiates peristalsis in the form of a **migrating motility complex**. These complexes, which begin in the duodenum, force chyme through a short section of the small intestine and then stop. The next contraction begins a little bit farther down than the first, forces chyme a bit farther through the small intestine, then stops. These complexes move slowly down the small intestine, forcing chyme on the way, taking around 90 to 120 minutes to finally reach the end of the ileum. At this point, the process is repeated, starting in the duodenum.

The ileocecal valve, a sphincter, is usually in a constricted state, but when motility in the ileum increases, this sphincter relaxes, allowing food residue to enter the first portion of the large intestine, the cecum. Relaxation of the ileocecal sphincter is controlled by both nerves and hormones. First,

digestive activity in the stomach provokes the **gastroileal reflex**, which increases the force of ileal segmentation. Second, the stomach releases the hormone gastrin, which enhances ileal motility, thus relaxing the ileocecal sphincter. After chyme passes through, backward pressure helps close the sphincter, preventing backflow into the ileum. Because of this reflex, your lunch is completely emptied from your stomach and small intestine by the time you eat your dinner. It takes about 3 to 5 hours for all chyme to leave the small intestine.

Chemical Digestion in the Small Intestine

The digestion of proteins and carbohydrates, which partially occurs in the stomach, is completed in the small intestine with the aid of intestinal and pancreatic juices. Lipids arrive in the intestine largely undigested, so much of the focus here is on lipid digestion, which is facilitated by bile and the enzyme pancreatic lipase.

Moreover, intestinal juice combines with pancreatic juice to provide a liquid medium that facilitates absorption. The intestine is also where most water is absorbed, via osmosis. The small intestine's absorptive cells also synthesize digestive enzymes and then place them in the plasma membranes of the microvilli. This distinguishes the small intestine from the stomach; that is, enzymatic digestion occurs not only in the lumen, but also on the luminal surfaces of the mucosal cells.

For optimal chemical digestion, chyme must be delivered from the stomach slowly and in small amounts. This is because chyme from the stomach is typically hypertonic, and if large quantities were forced all at once into the small intestine, the resulting osmotic water loss from the blood into the intestinal lumen would result in potentially life-threatening low blood volume. In addition, continued digestion requires an upward adjustment of the low pH of stomach chyme, along with rigorous mixing of the chyme with bile and pancreatic juices. Both processes take time, so the pumping action of the pylorus must be carefully controlled to prevent the duodenum from being overwhelmed with chyme.

Note:

Disorders of the...

Small Intestine: Lactose Intolerance

Lactose intolerance is a condition characterized by indigestion caused by dairy products. It occurs when the absorptive cells of the small intestine do not produce enough lactase, the enzyme that digests the milk sugar lactose. In most mammals, lactose intolerance increases with age. In contrast, some human populations, most notably Caucasians, are able to maintain the ability to produce lactase as adults.

In people with lactose intolerance, the lactose in chyme is not digested. Bacteria in the large intestine ferment the undigested lactose, a process that produces gas. In addition to gas, symptoms include abdominal cramps, bloating, and diarrhea. Symptom severity ranges from mild discomfort to severe pain; however, symptoms resolve once the lactose is eliminated in feces.

The hydrogen breath test is used to help diagnose lactose intolerance. Lactose-tolerant people have very little hydrogen in their breath. Those with lactose intolerance exhale hydrogen, which is one of the gases produced by the bacterial fermentation of lactose in the colon. After the hydrogen is absorbed from the intestine, it is transported through blood vessels into the lungs. There are a number of lactose-free dairy products available in grocery stores. In addition, dietary supplements are available. Taken with food, they provide lactase to help digest lactose.

The Large Intestine

The **large intestine** is the terminal part of the alimentary canal. The primary function of this organ is to finish absorption of nutrients and water, synthesize certain vitamins, form feces, and eliminate feces from the body.

Structure

The large intestine runs from the appendix to the anus. It frames the small intestine on three sides. Despite its being about one-half as long as the small

intestine, it is called large because it is more than twice the diameter of the small intestine, about 3 inches.

Subdivisions

The large intestine is subdivided into four main regions: the cecum, the colon, the rectum, and the anus. The ileocecal valve, located at the opening between the ileum and the large intestine, controls the flow of chyme from the small intestine to the large intestine.

Cecum

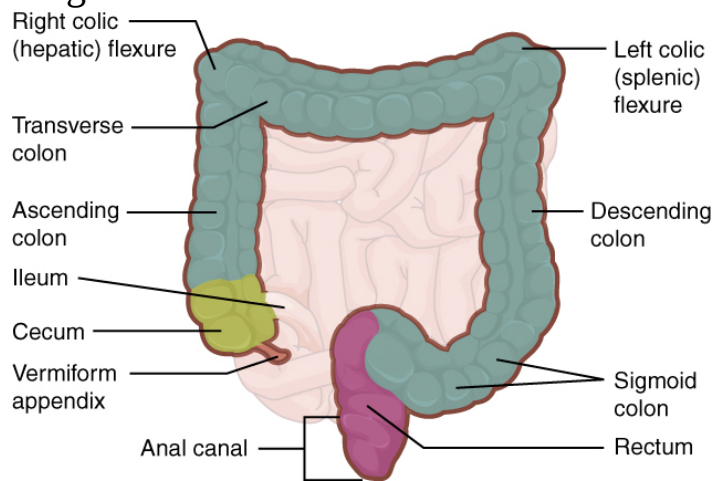
The first part of the large intestine is the **cecum**, a sac-like structure that is suspended inferior to the ileocecal valve. It is about 6 cm (2.4 in) long, receives the contents of the ileum, and continues the absorption of water and salts. The **appendix** (or vermiform appendix) is a winding tube that attaches to the cecum. Although the 7.6-cm (3-in) long appendix contains lymphoid tissue, suggesting an immunologic function, this organ is generally considered vestigial. However, at least one recent report postulates a survival advantage conferred by the appendix: In diarrheal illness, the appendix may serve as a bacterial reservoir to repopulate the enteric bacteria for those surviving the initial phases of the illness. Moreover, its twisted anatomy provides a haven for the accumulation and multiplication of enteric bacteria. The **mesoappendix**, the mesentery of the appendix, tethers it to the mesentery of the ileum.

Colon

The cecum blends seamlessly with the **colon**. Upon entering the colon, the food residue first travels up the **ascending colon** on the right side of the abdomen. At the inferior surface of the liver, the colon bends to form the **right colic flexure** (hepatic flexure) and becomes the **transverse colon**. The region defined as hindgut begins with the last third of the transverse

colon and continues on. Food residue passing through the transverse colon travels across to the left side of the abdomen, where the colon angles sharply immediately inferior to the spleen, at the **left colic flexure** (splenic flexure). From there, food residue passes through the **descending colon**, which runs down the left side of the posterior abdominal wall. After entering the pelvis inferiorly, it becomes the s-shaped **sigmoid colon**, which extends medially to the midline ([\[link\]](#)). The ascending and descending colon, and the rectum (discussed next) are located in the retroperitoneum. The transverse and sigmoid colon are tethered to the posterior abdominal wall by the mesocolon.

Large Intestine



The large intestine includes the cecum, colon, and rectum.

Note:

Homeostatic Imbalances

Colorectal Cancer

Each year, approximately 140,000 Americans are diagnosed with colorectal cancer, and another 49,000 die from it, making it one of the most deadly malignancies. People with a family history of colorectal cancer are at increased risk. Smoking, excessive alcohol consumption, and a diet high in animal fat and protein also increase the risk. Despite popular opinion to

the contrary, studies support the conclusion that dietary fiber and calcium do not reduce the risk of colorectal cancer.

Colorectal cancer may be signaled by constipation or diarrhea, cramping, abdominal pain, and rectal bleeding. Bleeding from the rectum may be either obvious or occult (hidden in feces). Since most colon cancers arise from benign mucosal growths called polyps, cancer prevention is focused on identifying these polyps. The colonoscopy is both diagnostic and therapeutic. Colonoscopy not only allows identification of precancerous polyps, the procedure also enables them to be removed before they become malignant. Screening for fecal occult blood tests and colonoscopy is recommended for those over 50 years of age.

Rectum

Food residue leaving the sigmoid colon enters the **rectum** in the pelvis, near the third sacral vertebra. The final 20.3 cm (8 in) of the alimentary canal, the rectum extends anterior to the sacrum and coccyx. Even though rectum is Latin for “straight,” this structure follows the curved contour of the sacrum and has three lateral bends that create a trio of internal transverse folds called the **rectal valves**. These valves help separate the feces from gas to prevent the simultaneous passage of feces and gas.

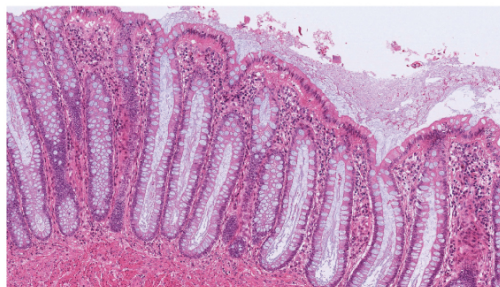
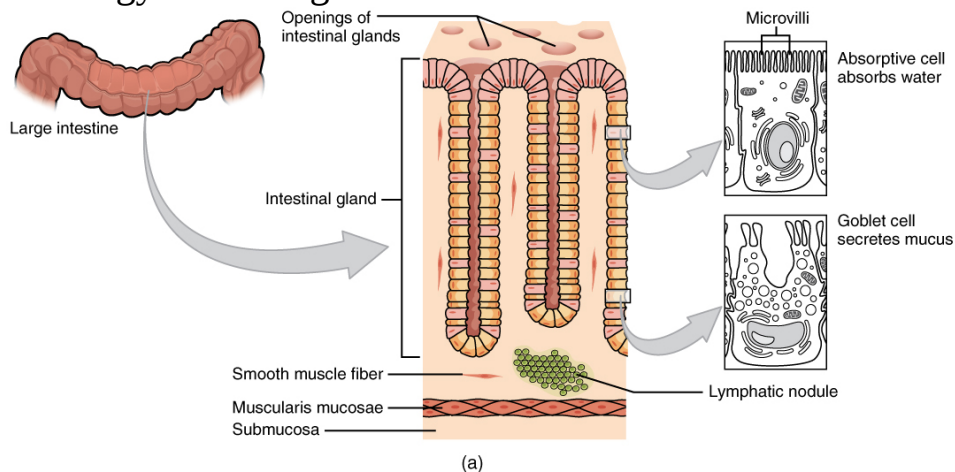
Anal Canal

Finally, food residue reaches the last part of the large intestine, the **anal canal**, which is located in the perineum, completely outside of the abdominopelvic cavity. This 3.8–5 cm (1.5–2 in) long structure opens to the exterior of the body at the anus. The anal canal includes two sphincters. The **internal anal sphincter** is made of smooth muscle, and its contractions are involuntary. The **external anal sphincter** is made of skeletal muscle, which is under voluntary control. Except when defecating, both usually remain closed.

Histology

There are several notable differences between the walls of the large and small intestines ([link](#)). For example, few enzyme-secreting cells are found in the wall of the large intestine, and there are no circular folds or villi. Other than in the anal canal, the mucosa of the colon is simple columnar epithelium made mostly of enterocytes (absorptive cells) and goblet cells. In addition, the wall of the large intestine has far more intestinal glands, which contain a vast population of enterocytes and goblet cells. These goblet cells secrete mucus that eases the movement of feces and protects the intestine from the effects of the acids and gases produced by enteric bacteria. The enterocytes absorb water and salts as well as vitamins produced by your intestinal bacteria.

Histology of the large Intestine



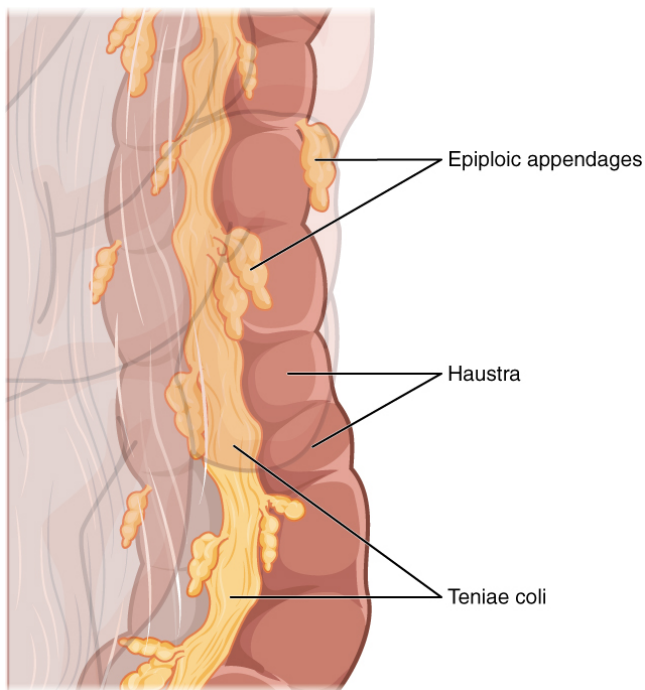
(a) The histologies of the large intestine and small intestine (not shown) are adapted for the digestive functions of each organ. (b) This micrograph shows the colon's simple columnar epithelium and goblet

cells. LM x 464. (credit b: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Anatomy

Three features are unique to the large intestine: teniae coli, haustra, and epiploic appendages ([link](#)). The **teniae coli** are three bands of smooth muscle that make up the longitudinal muscle layer of the muscularis of the large intestine, except at its terminal end. Tonic contractions of the teniae coli bunch up the colon into a succession of pouches called **haustra** (singular = haustrum), which are responsible for the wrinkled appearance of the colon. Attached to the teniae coli are small, fat-filled sacs of visceral peritoneum called **epiploic appendages**. The purpose of these is unknown. Although the rectum and anal canal have neither teniae coli nor haustra, they do have well-developed layers of muscularis that create the strong contractions needed for defecation.

Teniae Coli, Haustra, and Epiploic Appendages



The stratified squamous epithelial mucosa of the anal canal connects to the skin on the outside of the anus. This mucosa varies considerably from that of the rest of the colon to accommodate the high level of abrasion as feces pass through. The anal canal's mucous membrane is organized into longitudinal folds, each called an **anal column**, which house a grid of arteries and veins. Two superficial venous plexuses are found in the anal canal: one within the anal columns and one at the anus.

Depressions between the anal columns, each called an **anal sinus**, secrete mucus that facilitates defecation. The **pectinate line** (or dentate line) is a horizontal, jagged band that runs circumferentially just below the level of the anal sinuses, and represents the junction between the hindgut and external skin. The mucosa above this line is fairly insensitive, whereas the area below is very sensitive. The resulting difference in pain threshold is due to the fact that the upper region is innervated by visceral sensory fibers, and the lower region is innervated by somatic sensory fibers.

Bacterial Flora

Most bacteria that enter the alimentary canal are killed by lysozyme, defensins, HCl, or protein-digesting enzymes. However, trillions of bacteria live within the large intestine and are referred to as the **bacterial flora**. Most of the more than 700 species of these bacteria are nonpathogenic commensal organisms that cause no harm as long as they stay in the gut lumen. In fact, many facilitate chemical digestion and absorption, and some synthesize certain vitamins, mainly biotin, pantothenic acid, and vitamin K. Some are linked to increased immune response. A refined system prevents these bacteria from crossing the mucosal barrier. First, peptidoglycan, a component of bacterial cell walls, activates the release of chemicals by the mucosa's epithelial cells, which draft immune cells, especially dendritic cells, into the mucosa. Dendritic cells open the tight junctions between epithelial cells and extend probes into the lumen to evaluate the microbial antigens. The dendritic cells with antigens then travel to neighboring lymphoid follicles in the mucosa where T cells inspect for antigens. This process triggers an IgA-mediated response, if warranted, in the lumen that

blocks the commensal organisms from infiltrating the mucosa and setting off a far greater, widespread systematic reaction.

Digestive Functions of the Large Intestine

The residue of chyme that enters the large intestine contains few nutrients except water, which is reabsorbed as the residue lingers in the large intestine, typically for 12 to 24 hours. Thus, it may not surprise you that the large intestine can be completely removed without significantly affecting digestive functioning. For example, in severe cases of inflammatory bowel disease, the large intestine can be removed by a procedure known as a colectomy. Often, a new fecal pouch can be crafted from the small intestine and sutured to the anus, but if not, an ileostomy can be created by bringing the distal ileum through the abdominal wall, allowing the watery chyme to be collected in a bag-like adhesive appliance.

Mechanical Digestion

In the large intestine, mechanical digestion begins when chyme moves from the ileum into the cecum, an activity regulated by the ileocecal sphincter. Right after you eat, peristalsis in the ileum forces chyme into the cecum. When the cecum is distended with chyme, contractions of the ileocecal sphincter strengthen. Once chyme enters the cecum, colon movements begin.

Mechanical digestion in the large intestine includes a combination of three types of movements. The presence of food residues in the colon stimulates a slow-moving **haustral contraction**. This type of movement involves sluggish segmentation, primarily in the transverse and descending colons. When a haustrum is distended with chyme, its muscle contracts, pushing the residue into the next haustrum. These contractions occur about every 30 minutes, and each last about 1 minute. These movements also mix the food residue, which helps the large intestine absorb water. The second type of movement is peristalsis, which, in the large intestine, is slower than in the more proximal portions of the alimentary canal. The third type is a **mass**

movement. These strong waves start midway through the transverse colon and quickly force the contents toward the rectum. Mass movements usually occur three or four times per day, either while you eat or immediately afterward. Distension in the stomach and the breakdown products of digestion in the small intestine provoke the **gastrocolic reflex**, which increases motility, including mass movements, in the colon. Fiber in the diet both softens the stool and increases the power of colonic contractions, optimizing the activities of the colon.

Chemical Digestion

Although the glands of the large intestine secrete mucus, they do not secrete digestive enzymes. Therefore, chemical digestion in the large intestine occurs exclusively because of bacteria in the lumen of the colon. Through the process of **saccharolytic fermentation**, bacteria break down some of the remaining carbohydrates. This results in the discharge of hydrogen, carbon dioxide, and methane gases that create **flatus** (gas) in the colon; flatulence is excessive flatus. Each day, up to 1500 mL of flatus is produced in the colon. More is produced when you eat foods such as beans, which are rich in otherwise indigestible sugars and complex carbohydrates like soluble dietary fiber.

Absorption, Feces Formation, and Defecation

The small intestine absorbs about 90 percent of the water you ingest (either as liquid or within solid food). The large intestine absorbs most of the remaining water, a process that converts the liquid chyme residue into semisolid **feces** (“stool”). Feces is composed of undigested food residues, unabsorbed digested substances, millions of bacteria, old epithelial cells from the GI mucosa, inorganic salts, and enough water to let it pass smoothly out of the body. Of every 500 mL (17 ounces) of food residue that enters the cecum each day, about 150 mL (5 ounces) become feces.

Feces are eliminated through contractions of the rectal muscles. You help this process by a voluntary procedure called **Valsalva’s maneuver**, in

which you increase intra-abdominal pressure by contracting your diaphragm and abdominal wall muscles, and closing your glottis.

The process of defecation begins when mass movements force feces from the colon into the rectum, stretching the rectal wall and provoking the defecation reflex, which eliminates feces from the rectum. This parasympathetic reflex is mediated by the spinal cord. It contracts the sigmoid colon and rectum, relaxes the internal anal sphincter, and initially contracts the external anal sphincter. The presence of feces in the anal canal sends a signal to the brain, which gives you the choice of voluntarily opening the external anal sphincter (defecating) or keeping it temporarily closed. If you decide to delay defecation, it takes a few seconds for the reflex contractions to stop and the rectal walls to relax. The next mass movement will trigger additional defecation reflexes until you defecate.

If defecation is delayed for an extended time, additional water is absorbed, making the feces firmer and potentially leading to constipation. On the other hand, if the waste matter moves too quickly through the intestines, not enough water is absorbed, and diarrhea can result. This can be caused by the ingestion of foodborne pathogens. In general, diet, health, and stress determine the frequency of bowel movements. The number of bowel movements varies greatly between individuals, ranging from two or three per day to three or four per week.

Note:



By watching this [animation](#) you will see that for the various food groups—proteins, fats, and carbohydrates—digestion begins in different parts of the digestion system, though all end in the same place. Of the three major food

classes (carbohydrates, fats, and proteins), which is digested in the mouth, the stomach, and the small intestine?

Chapter Review

The three main regions of the small intestine are the duodenum, the jejunum, and the ileum. The small intestine is where digestion is completed and virtually all absorption occurs. These two activities are facilitated by structural adaptations that increase the mucosal surface area by 600-fold, including circular folds, villi, and microvilli. There are around 200 million microvilli per square millimeter of small intestine, which contain brush border enzymes that complete the digestion of carbohydrates and proteins. Combined with pancreatic juice, intestinal juice provides the liquid medium needed to further digest and absorb substances from chyme. The small intestine is also the site of unique mechanical digestive movements. Segmentation moves the chyme back and forth, increasing mixing and opportunities for absorption. Migrating motility complexes propel the residual chyme toward the large intestine.

The main regions of the large intestine are the cecum, the colon, and the rectum. The large intestine absorbs water and forms feces, and is responsible for defecation. Bacterial flora break down additional carbohydrate residue, and synthesize certain vitamins. The mucosa of the large intestinal wall is generously endowed with goblet cells, which secrete mucus that eases the passage of feces. The entry of feces into the rectum activates the defecation reflex.

Interactive Link Questions

Exercise:

Problem:

Watch this [animation](#) that depicts the structure of the small intestine, and, in particular, the villi. Epithelial cells continue the digestion and absorption of nutrients and transport these nutrients to the lymphatic and circulatory systems. In the small intestine, the products of food digestion are absorbed by different structures in the villi. Which structure absorbs and transports fats?

Solution:

Answers may vary.

Exercise:**Problem:**

By watching this [animation](#), you will see that for the various food groups—proteins, fats, and carbohydrates—digestion begins in different parts of the digestion system, though all end in the same place. Of the three major food classes (carbohydrates, fats, and proteins), which is digested in the mouth, the stomach, and the small intestine?

Solution:

Answers may vary.

Review Questions**Exercise:****Problem:**

In which part of the alimentary canal does most digestion occur?

- a. stomach
- b. proximal small intestine

- c. distal small intestine
 - d. ascending colon
-

Solution:

B

Exercise:

Problem: Which of these is most associated with villi?

- a. haustra
 - b. lacteals
 - c. bacterial flora
 - d. intestinal glands
-

Solution:

B

Exercise:

Problem: What is the role of the small intestine's MALT?

- a. secreting mucus
 - b. buffering acidic chyme
 - c. activating pepsin
 - d. preventing bacteria from entering the bloodstream
-

Solution:

D

Exercise:

Problem: Which part of the large intestine attaches to the appendix?

- a. cecum
 - b. ascending colon
 - c. transverse colon
 - d. descending colon
-

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

Explain how nutrients absorbed in the small intestine pass into the general circulation.

Solution:

Nutrients from the breakdown of carbohydrates and proteins are absorbed through a capillary bed in the villi of the small intestine. Lipid breakdown products are absorbed into a lacteal in the villi, and transported via the lymphatic system to the bloodstream.

Exercise:

Problem:

Why is it important that chyme from the stomach is delivered to the small intestine slowly and in small amounts?

Solution:

If large quantities of chyme were forced into the small intestine, it would result in osmotic water loss from the blood into the intestinal lumen that could cause potentially life-threatening low blood volume and erosion of the duodenum.

Exercise:

Problem:

Describe three of the differences between the walls of the large and small intestines.

Solution:

The mucosa of the small intestine includes circular folds, villi, and microvilli. The wall of the large intestine has a thick mucosal layer, and deeper and more abundant mucus-secreting glands that facilitate the smooth passage of feces. There are three features that are unique to the large intestine: teniae coli, haustra, and epiploic appendages.

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Centers for Disease Control and Prevention (US). Morbidity and mortality weekly report: notifiable diseases and mortality tables [Internet]. Atlanta (GA); [cited 2013 Apr 3]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101md.htm?s_cid=mm6101md_w.

Glossary

anal canal

final segment of the large intestine

anal column

long fold of mucosa in the anal canal

anal sinus

recess between anal columns

appendix

(vermiform appendix) coiled tube attached to the cecum

ascending colon

first region of the colon

bacterial flora

bacteria in the large intestine

brush border

fuzzy appearance of the small intestinal mucosa created by microvilli

cecum

pouch forming the beginning of the large intestine

circular fold

(also, plica circulare) deep fold in the mucosa and submucosa of the small intestine

colon

part of the large intestine between the cecum and the rectum

descending colon

part of the colon between the transverse colon and the sigmoid colon

duodenal gland

(also, Brunner's gland) mucous-secreting gland in the duodenal submucosa

duodenum

first part of the small intestine, which starts at the pyloric sphincter and ends at the jejunum

epiploic appendage

small sac of fat-filled visceral peritoneum attached to teniae coli

external anal sphincter

voluntary skeletal muscle sphincter in the anal canal

feces

semisolid waste product of digestion

flatus

gas in the intestine

gastrocolic reflex

propulsive movement in the colon activated by the presence of food in the stomach

gastroileal reflex

long reflex that increases the strength of segmentation in the ileum

hastrum

small pouch in the colon created by tonic contractions of teniae coli

haustral contraction

slow segmentation in the large intestine

hepatopancreatic ampulla

(also, ampulla of Vater) bulb-like point in the wall of the duodenum where the bile duct and main pancreatic duct unite

hepatopancreatic sphincter

(also, sphincter of Oddi) sphincter regulating the flow of bile and pancreatic juice into the duodenum

ileocecal sphincter

sphincter located where the small intestine joins with the large intestine

ileum

end of the small intestine between the jejunum and the large intestine

internal anal sphincter

involuntary smooth muscle sphincter in the anal canal

intestinal gland

(also, crypt of Lieberkühn) gland in the small intestinal mucosa that secretes intestinal juice

intestinal juice

mixture of water and mucus that helps absorb nutrients from chyme

jejunum

middle part of the small intestine between the duodenum and the ileum

lacteal

lymphatic capillary in the villi

large intestine

terminal portion of the alimentary canal

left colic flexure

(also, splenic flexure) point where the transverse colon curves below the inferior end of the spleen

main pancreatic duct

(also, duct of Wirsung) duct through which pancreatic juice drains from the pancreas

major duodenal papilla

point at which the hepatopancreatic ampulla opens into the duodenum

mass movement

long, slow, peristaltic wave in the large intestine

mesoappendix

mesentery of the appendix

microvillus

small projection of the plasma membrane of the absorptive cells of the small intestinal mucosa

migrating motility complex

form of peristalsis in the small intestine

motilin

hormone that initiates migrating motility complexes

pectinate line

horizontal line that runs like a ring, perpendicular to the inferior margins of the anal sinuses

rectal valve

one of three transverse folds in the rectum where feces is separated from flatus

rectum

part of the large intestine between the sigmoid colon and anal canal

right colic flexure

(also, hepatic flexure) point, at the inferior surface of the liver, where the ascending colon turns abruptly to the left

saccharolytic fermentation

anaerobic decomposition of carbohydrates

sigmoid colon

end portion of the colon, which terminates at the rectum

small intestine

section of the alimentary canal where most digestion and absorption occurs

tenia coli

one of three smooth muscle bands that make up the longitudinal muscle layer of the muscularis in all of the large intestine except the

terminal end

transverse colon

part of the colon between the ascending colon and the descending colon

Valsalva's maneuver

voluntary contraction of the diaphragm and abdominal wall muscles and closing of the glottis, which increases intra-abdominal pressure and facilitates defecation

villus

projection of the mucosa of the small intestine

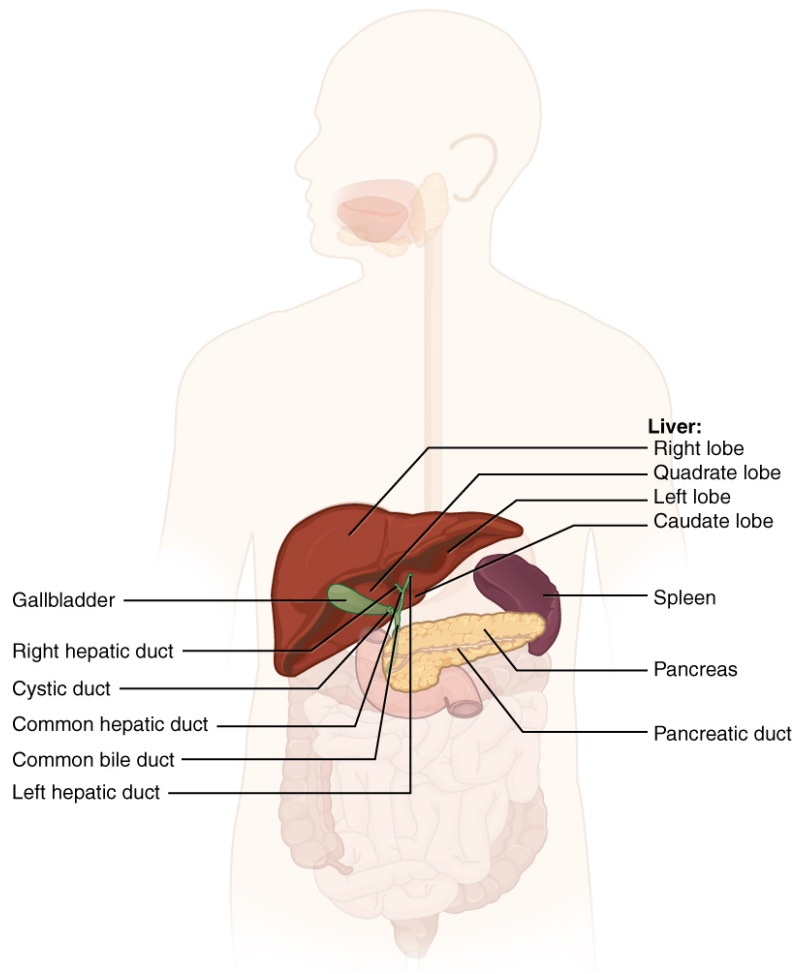
Accessory Organs in Digestion: The Liver, Pancreas, and Gallbladder

By the end of this section, you will be able to:

- State the main digestive roles of the liver, pancreas, and gallbladder
- Identify three main features of liver histology that are critical to its function
- Discuss the composition and function of bile
- Identify the major types of enzymes and buffers present in pancreatic juice

Chemical digestion in the small intestine relies on the activities of three accessory digestive organs: the liver, pancreas, and gallbladder ([\[link\]](#)). The digestive role of the liver is to produce bile and export it to the duodenum. The gallbladder primarily stores, concentrates, and releases bile. The pancreas produces pancreatic juice, which contains digestive enzymes and bicarbonate ions, and delivers it to the duodenum.

Accessory Organs



The liver, pancreas, and gallbladder are considered accessory digestive organs, but their roles in the digestive system are vital.

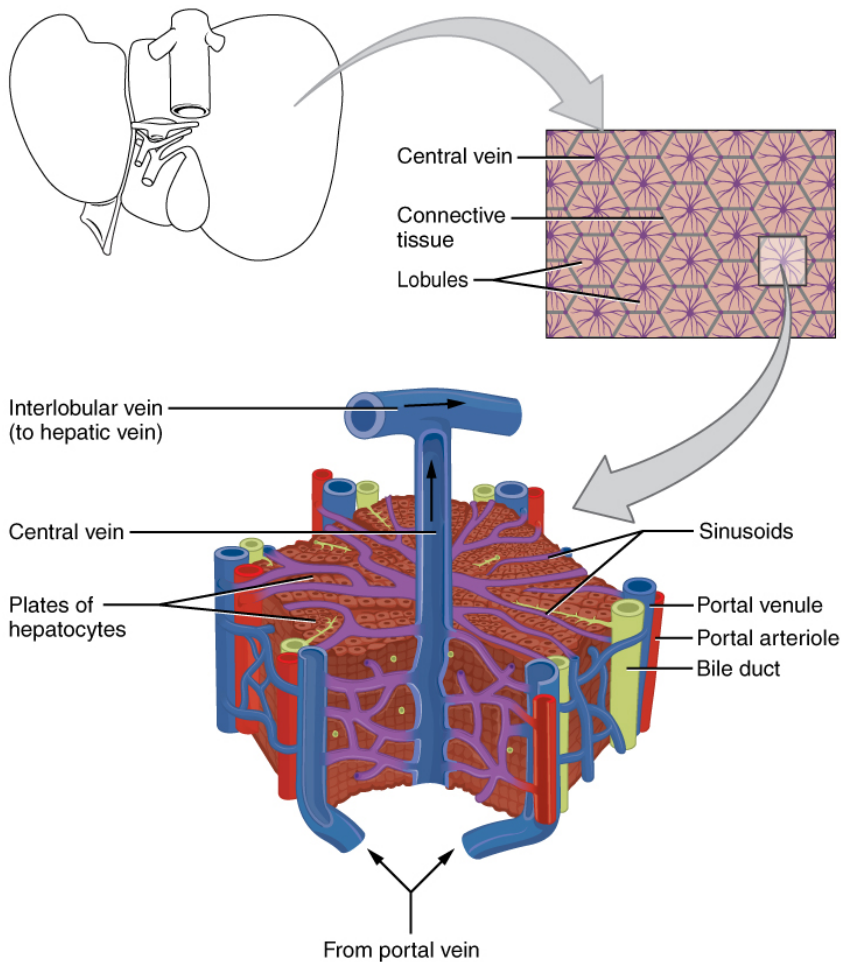
The Liver

The **liver** is the largest gland in the body, weighing about three pounds in an adult. It is also one of the most important organs. In addition to being an accessory digestive organ, it plays a number of roles in metabolism and regulation. The liver lies inferior to the diaphragm in the right upper quadrant of the abdominal cavity and receives protection from the surrounding ribs.

The liver is divided into two primary lobes: a large right lobe and a much smaller left lobe. In the right lobe, some anatomists also identify an inferior quadrate lobe and a posterior caudate lobe, which are defined by internal features. The liver is connected to the abdominal wall and diaphragm by five peritoneal folds referred to as ligaments. These are the falciform ligament, the coronary ligament, two lateral ligaments, and the ligamentum teres hepatis. The falciform ligament and ligamentum teres hepatis are actually remnants of the umbilical vein, and separate the right and left lobes anteriorly. The lesser omentum tethers the liver to the lesser curvature of the stomach.

The **porta hepatis** (“gate to the liver”) is where the **hepatic artery** and **hepatic portal vein** enter the liver. These two vessels, along with the common hepatic duct, run behind the lateral border of the lesser omentum on the way to their destinations. As shown in [\[link\]](#), the hepatic artery delivers oxygenated blood from the heart to the liver. The hepatic portal vein delivers partially deoxygenated blood containing nutrients absorbed from the small intestine and actually supplies more oxygen to the liver than do the much smaller hepatic arteries. In addition to nutrients, drugs and toxins are also absorbed. After processing the bloodborne nutrients and toxins, the liver releases nutrients needed by other cells back into the blood, which drains into the central vein and then through the hepatic vein to the inferior vena cava. With this hepatic portal circulation, all blood from the alimentary canal passes through the liver. This largely explains why the liver is the most common site for the metastasis of cancers that originate in the alimentary canal.

Microscopic Anatomy of the Liver



The liver receives oxygenated blood from the hepatic artery and nutrient-rich deoxygenated blood from the hepatic portal vein.

Histology

The liver has three main components: hepatocytes, bile canaliculi, and hepatic sinusoids. A **hepatocyte** is the liver's main cell type, accounting for around 80 percent of the liver's volume. These cells play a role in a wide variety of secretory, metabolic, and endocrine functions. Plates of

hepatocytes called hepatic laminae radiate outward from the portal vein in each **hepatic lobule**.

Between adjacent hepatocytes, grooves in the cell membranes provide room for each **bile canaliculus** (plural = canaliculi). These small ducts accumulate the bile produced by hepatocytes. From here, bile flows first into bile ductules and then into bile ducts. The bile ducts unite to form the larger right and left hepatic ducts, which themselves merge and exit the liver as the **common hepatic duct**. This duct then joins with the cystic duct from the gallbladder, forming the **common bile duct** through which bile flows into the small intestine.

A **hepatic sinusoid** is an open, porous blood space formed by fenestrated capillaries from nutrient-rich hepatic portal veins and oxygen-rich hepatic arteries. Hepatocytes are tightly packed around the fenestrated endothelium of these spaces, giving them easy access to the blood. From their central position, hepatocytes process the nutrients, toxins, and waste materials carried by the blood. Materials such as bilirubin are processed and excreted into the bile canaliculi. Other materials including proteins, lipids, and carbohydrates are processed and secreted into the sinusoids or just stored in the cells until called upon. The hepatic sinusoids combine and send blood to a **central vein**. Blood then flows through a **hepatic vein** into the inferior vena cava. This means that blood and bile flow in opposite directions. The hepatic sinusoids also contain star-shaped **reticuloendothelial cells** (Kupffer cells), phagocytes that remove dead red and white blood cells, bacteria, and other foreign material that enter the sinusoids. The **portal triad** is a distinctive arrangement around the perimeter of hepatic lobules, consisting of three basic structures: a bile duct, a hepatic artery branch, and a hepatic portal vein branch.

Bile

Recall that lipids are hydrophobic, that is, they do not dissolve in water. Thus, before they can be digested in the watery environment of the small intestine, large lipid globules must be broken down into smaller lipid

globules, a process called emulsification. **Bile** is a mixture secreted by the liver to accomplish the emulsification of lipids in the small intestine.

Hepatocytes secrete about one liter of bile each day. A yellow-brown or yellow-green alkaline solution (pH 7.6 to 8.6), bile is a mixture of water, bile salts, bile pigments, phospholipids (such as lecithin), electrolytes, cholesterol, and triglycerides. The components most critical to emulsification are bile salts and phospholipids, which have a nonpolar (hydrophobic) region as well as a polar (hydrophilic) region. The hydrophobic region interacts with the large lipid molecules, whereas the hydrophilic region interacts with the watery chyme in the intestine. This results in the large lipid globules being pulled apart into many tiny lipid fragments of about 1 μm in diameter. This change dramatically increases the surface area available for lipid-digesting enzyme activity. This is the same way dish soap works on fats mixed with water.

Bile salts act as emulsifying agents, so they are also important for the absorption of digested lipids. While most constituents of bile are eliminated in feces, bile salts are reclaimed by the **enterohepatic circulation**. Once bile salts reach the ileum, they are absorbed and returned to the liver in the hepatic portal blood. The hepatocytes then excrete the bile salts into newly formed bile. Thus, this precious resource is recycled.

Bilirubin, the main bile pigment, is a waste product produced when the spleen removes old or damaged red blood cells from the circulation. These breakdown products, including proteins, iron, and toxic bilirubin, are transported to the liver via the splenic vein of the hepatic portal system. In the liver, proteins and iron are recycled, whereas bilirubin is excreted in the bile. It accounts for the green color of bile. Bilirubin is eventually transformed by intestinal bacteria into stercobilin, a brown pigment that gives your stool its characteristic color! In some disease states, bile does not enter the intestine, resulting in white ('acholic') stool with a high fat content, since virtually no fats are broken down or absorbed.

Hepatocytes work non-stop, but bile production increases when fatty chyme enters the duodenum and stimulates the secretion of the gut hormone secretin. Between meals, bile is produced but conserved. The valve-like

hepatopancreatic ampulla closes, allowing bile to divert to the gallbladder, where it is concentrated and stored until the next meal.

Note:

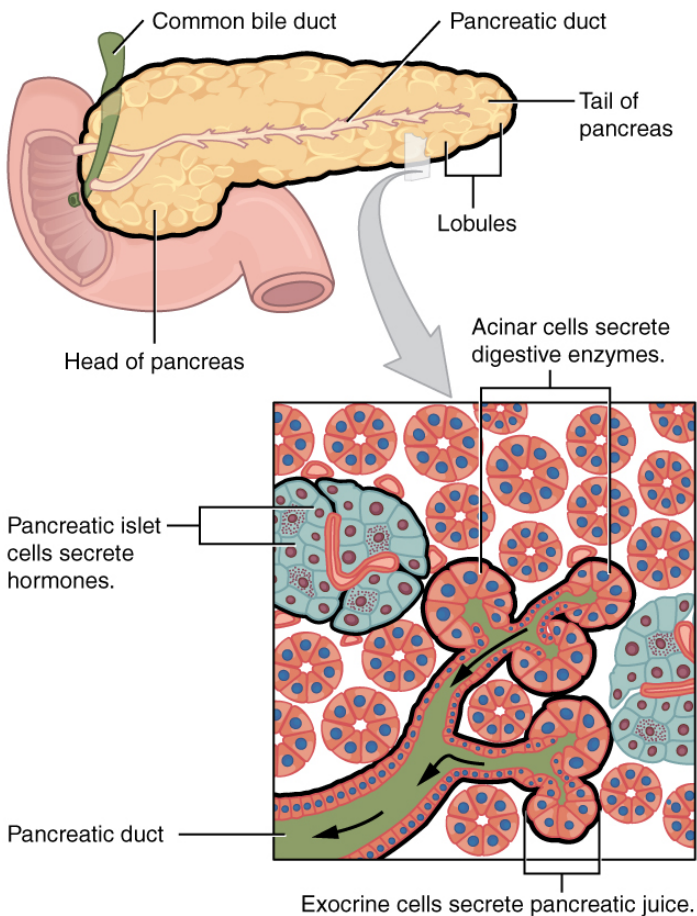


Watch this [video](#) to see the structure of the liver and how this structure supports the functions of the liver, including the processing of nutrients, toxins, and wastes. At rest, about 1500 mL of blood per minute flow through the liver. What percentage of this blood flow comes from the hepatic portal system?

The Pancreas

The soft, oblong, glandular **pancreas** lies transversely in the retroperitoneum behind the stomach. Its head is nestled into the “c-shaped” curvature of the duodenum with the body extending to the left about 15.2 cm (6 in) and ending as a tapering tail in the hilum of the spleen. It is a curious mix of exocrine (secreting digestive enzymes) and endocrine (releasing hormones into the blood) functions ([link](#)).

Exocrine and Endocrine Pancreas



The pancreas has a head, a body, and a tail. It delivers pancreatic juice to the duodenum through the pancreatic duct.

The exocrine part of the pancreas arises as little grape-like cell clusters, each called an **acinus** (plural = acini), located at the terminal ends of pancreatic ducts. These acinar cells secrete enzyme-rich **pancreatic juice** into tiny merging ducts that form two dominant ducts. The larger duct fuses with the common bile duct (carrying bile from the liver and gallbladder) just before entering the duodenum via a common opening (the hepatopancreatic ampulla). The smooth muscle sphincter of the hepatopancreatic ampulla controls the release of pancreatic juice and bile into the small intestine. The second and smaller pancreatic duct, the

accessory duct (duct of Santorini), runs from the pancreas directly into the duodenum, approximately 1 inch above the hepatopancreatic ampulla. When present, it is a persistent remnant of pancreatic development.

Scattered through the sea of exocrine acini are small islands of endocrine cells, the islets of Langerhans. These vital cells produce the hormones pancreatic polypeptide, insulin, glucagon, and somatostatin.

Pancreatic Juice

The pancreas produces over a liter of pancreatic juice each day. Unlike bile, it is clear and composed mostly of water along with some salts, sodium bicarbonate, and several digestive enzymes. Sodium bicarbonate is responsible for the slight alkalinity of pancreatic juice (pH 7.1 to 8.2), which serves to buffer the acidic gastric juice in chyme, inactivate pepsin from the stomach, and create an optimal environment for the activity of pH-sensitive digestive enzymes in the small intestine. Pancreatic enzymes are active in the digestion of sugars, proteins, and fats.

The pancreas produces protein-digesting enzymes in their inactive forms. These enzymes are activated in the duodenum. If produced in an active form, they would digest the pancreas (which is exactly what occurs in the disease, pancreatitis). The intestinal brush border enzyme **enteropeptidase** stimulates the activation of trypsin from trypsinogen of the pancreas, which in turn changes the pancreatic enzymes procarboxypeptidase and chymotrypsinogen into their active forms, carboxypeptidase and chymotrypsin.

The enzymes that digest starch (amylase), fat (lipase), and nucleic acids (nuclease) are secreted in their active forms, since they do not attack the pancreas as do the protein-digesting enzymes.

Pancreatic Secretion

Regulation of pancreatic secretion is the job of hormones and the parasympathetic nervous system. The entry of acidic chyme into the duodenum stimulates the release of secretin, which in turn causes the duct cells to release bicarbonate-rich pancreatic juice. The presence of proteins and fats in the duodenum stimulates the secretion of CCK, which then stimulates the acini to secrete enzyme-rich pancreatic juice and enhances the activity of secretin. Parasympathetic regulation occurs mainly during the cephalic and gastric phases of gastric secretion, when vagal stimulation prompts the secretion of pancreatic juice.

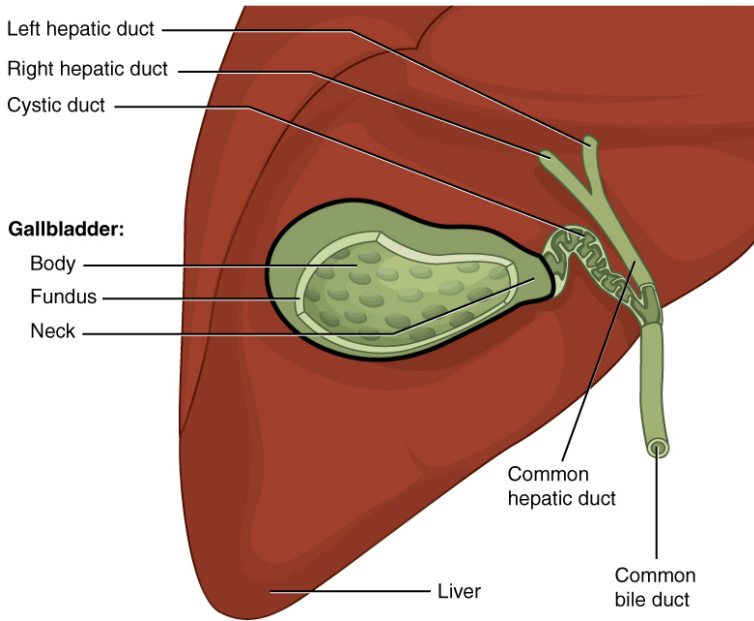
Usually, the pancreas secretes just enough bicarbonate to counterbalance the amount of HCl produced in the stomach. Hydrogen ions enter the blood when bicarbonate is secreted by the pancreas. Thus, the acidic blood draining from the pancreas neutralizes the alkaline blood draining from the stomach, maintaining the pH of the venous blood that flows to the liver.

The Gallbladder

The **gallbladder** is 8–10 cm (~3–4 in) long and is nested in a shallow area on the posterior aspect of the right lobe of the liver. This muscular sac stores, concentrates, and, when stimulated, propels the bile into the duodenum via the common bile duct. It is divided into three regions. The fundus is the widest portion and tapers medially into the body, which in turn narrows to become the neck. The neck angles slightly superiorly as it approaches the hepatic duct. The cystic duct is 1–2 cm (less than 1 in) long and turns inferiorly as it bridges the neck and hepatic duct.

The simple columnar epithelium of the gallbladder mucosa is organized in rugae, similar to those of the stomach. There is no submucosa in the gallbladder wall. The wall's middle, muscular coat is made of smooth muscle fibers. When these fibers contract, the gallbladder's contents are ejected through the **cystic duct** and into the bile duct ([\[link\]](#)). Visceral peritoneum reflected from the liver capsule holds the gallbladder against the liver and forms the outer coat of the gallbladder. The gallbladder's mucosa absorbs water and ions from bile, concentrating it by up to 10-fold.

Gallbladder



The gallbladder stores and concentrates bile, and releases it into the two-way cystic duct when it is needed by the small intestine.

Chapter Review

Chemical digestion in the small intestine cannot occur without the help of the liver and pancreas. The liver produces bile and delivers it to the common hepatic duct. Bile contains bile salts and phospholipids, which emulsify large lipid globules into tiny lipid droplets, a necessary step in lipid digestion and absorption. The gallbladder stores and concentrates bile, releasing it when it is needed by the small intestine.

The pancreas produces the enzyme- and bicarbonate-rich pancreatic juice and delivers it to the small intestine through ducts. Pancreatic juice buffers the acidic gastric juice in chyme, inactivates pepsin from the stomach, and enables the optimal functioning of digestive enzymes in the small intestine.

Interactive Link Questions

Exercise:**Problem:**

Watch this [video](#) to see the structure of the liver and how this structure supports the functions of the liver, including the processing of nutrients, toxins, and wastes. At rest, about 1500 mL of blood per minute flow through the liver. What percentage of this blood flow comes from the hepatic portal system?

Solution:

Answers may vary.

Review Questions**Exercise:**

Problem: Which of these statements about bile is true?

- a. About 500 mL is secreted daily.
 - b. Its main function is the denaturation of proteins.
 - c. It is synthesized in the gallbladder.
 - d. Bile salts are recycled.
-

Solution:

D

Exercise:

Problem: Pancreatic juice _____.

- a. deactivates bile.
- b. is secreted by pancreatic islet cells.
- c. buffers chyme.
- d. is released into the cystic duct.

Solution:

C

Critical Thinking Questions

Exercise:

Problem:

Why does the pancreas secrete some enzymes in their inactive forms, and where are these enzymes activated?

Solution:

The pancreas secretes protein-digesting enzymes in their inactive forms. If secreted in their active forms, they would self-digest the pancreas. These enzymes are activated in the duodenum.

Exercise:

Problem:

Describe the location of hepatocytes in the liver and how this arrangement enhances their function.

Solution:

The hepatocytes are the main cell type of the liver. They process, store, and release nutrients into the blood. Radiating out from the central vein, they are tightly packed around the hepatic sinusoids, allowing the hepatocytes easy access to the blood flowing through the sinusoids.

Glossary

accessory duct

(also, duct of Santorini) duct that runs from the pancreas into the duodenum

acinus

cluster of glandular epithelial cells in the pancreas that secretes pancreatic juice in the pancreas

bile

alkaline solution produced by the liver and important for the emulsification of lipids

bile canaliculus

small duct between hepatocytes that collects bile

bilirubin

main bile pigment, which is responsible for the brown color of feces

central vein

vein that receives blood from hepatic sinusoids

common bile duct

structure formed by the union of the common hepatic duct and the gallbladder's cystic duct

common hepatic duct

duct formed by the merger of the two hepatic ducts

cystic duct

duct through which bile drains and enters the gallbladder

enterohepatic circulation

recycling mechanism that conserves bile salts

enteropeptidase

intestinal brush-border enzyme that activates trypsinogen to trypsin

gallbladder

accessory digestive organ that stores and concentrates bile

hepatic artery

artery that supplies oxygenated blood to the liver

hepatic lobule

hexagonal-shaped structure composed of hepatocytes that radiate outward from a central vein

hepatic portal vein

vein that supplies deoxygenated nutrient-rich blood to the liver

hepatic sinusoid

blood capillaries between rows of hepatocytes that receive blood from the hepatic portal vein and the branches of the hepatic artery

hepatic vein

vein that drains into the inferior vena cava

hepatocytes

major functional cells of the liver

liver

largest gland in the body whose main digestive function is the production of bile

pancreas

accessory digestive organ that secretes pancreatic juice

pancreatic juice

secretion of the pancreas containing digestive enzymes and bicarbonate

porta hepatis

“gateway to the liver” where the hepatic artery and hepatic portal vein enter the liver

portal triad

bile duct, hepatic artery branch, and hepatic portal vein branch

reticuloendothelial cell

(also, Kupffer cell) phagocyte in hepatic sinusoids that filters out material from venous blood from the alimentary canal

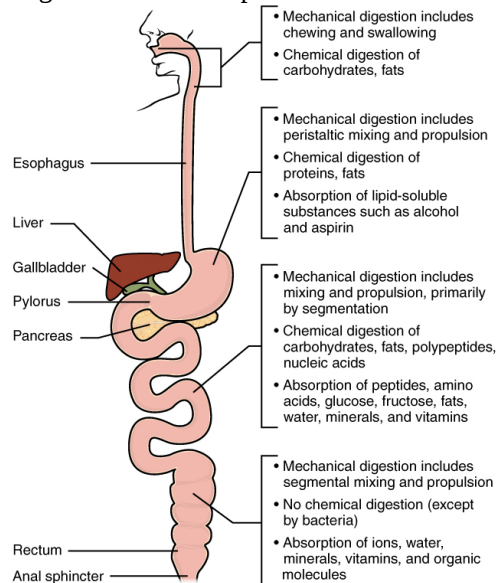
Chemical Digestion and Absorption: A Closer Look

By the end of this section, you will be able to:

- Identify the locations and primary secretions involved in the chemical digestion of carbohydrates, proteins, lipids, and nucleic acids
- Compare and contrast absorption of the hydrophilic and hydrophobic nutrients

As you have learned, the process of mechanical digestion is relatively simple. It involves the physical breakdown of food but does not alter its chemical makeup. Chemical digestion, on the other hand, is a complex process that reduces food into its chemical building blocks, which are then absorbed to nourish the cells of the body ([link](#)). In this section, you will look more closely at the processes of chemical digestion and absorption.

Digestion and Absorption



Digestion begins in the mouth and continues as food travels through the small intestine. Most absorption occurs in the small intestine.

Chemical Digestion

Large food molecules (for example, proteins, lipids, nucleic acids, and starches) must be broken down into subunits that are small enough to be absorbed by the lining of the alimentary canal. This is accomplished by enzymes through hydrolysis. The many enzymes involved in chemical digestion are summarized in [link](#).

The Digestive Enzymes

| The Digestive Enzymes | | | | |
|------------------------------|--------------------------------|-----------------|---|--|
| Enzyme Category | Enzyme Name | Source | Substrate | Product |
| Enzyme Category | Enzyme Name | Source | Substrate | Product |
| Salivary Enzymes | Lingual lipase | Lingual glands | Triglycerides | Free fatty acids, and mono- and diglycerides |
| Salivary Enzymes | Salivary amylase | Salivary glands | Polysaccharides | Disaccharides and trisaccharides |
| Gastric enzymes | Gastric lipase | Chief cells | Triglycerides | Fatty acids and monoacylglycerides |
| Gastric enzymes | Pepsin* | Chief cells | Proteins | Peptides |
| Brush border enzymes | α -Dextrinase | Small intestine | α -Dextrins | Glucose |
| Brush border enzymes | Enteropeptidase | Small intestine | Trypsinogen | Trypsin |
| Brush border enzymes | Lactase | Small intestine | Lactose | Glucose and galactose |
| Brush border enzymes | Maltase | Small intestine | Maltose | Glucose |
| Brush border enzymes | Nucleosidases and phosphatases | Small intestine | Nucleotides | Phosphates, nitrogenous bases, and pentoses |
| Brush border enzymes | Peptidases | Small intestine | Aminopeptidase: amino acids at the amino end of peptides Dipeptidase: dipeptides | Aminopeptidase: amino acids and peptides Dipeptidase: amino acids |
| Brush border enzymes | Sucrase | Small intestine | Sucrose | Glucose and fructose |

The Digestive Enzymes

| Enzyme Category | Enzyme Name | Source | Substrate | Product |
|--------------------|--------------------|-------------------------|--|---|
| Pancreatic enzymes | Carboxy-peptidase* | Pancreatic acinar cells | Amino acids at the carboxyl end of peptides | Amino acids and peptides |
| Pancreatic enzymes | Chymotrypsin* | Pancreatic acinar cells | Proteins | Peptides |
| Pancreatic enzymes | Elastase* | Pancreatic acinar cells | Proteins | Peptides |
| Pancreatic enzymes | Nucleases | Pancreatic acinar cells | Ribonuclease: ribonucleic acids Deoxyribonuclease: deoxyribonucleic acids | Nucleotides |
| Pancreatic enzymes | Pancreatic amylase | Pancreatic acinar cells | Polysaccharides (starches) | α -Dextrins, disaccharides (maltose), trisaccharides (maltotriose) |
| Pancreatic enzymes | Pancreatic lipase | Pancreatic acinar cells | Triglycerides that have been emulsified by bile salts | Fatty acids and monoacylglycerides |
| Pancreatic enzymes | Trypsin* | Pancreatic acinar cells | Proteins | Peptides |

*These enzymes have been activated by other substances.

Carbohydrate Digestion

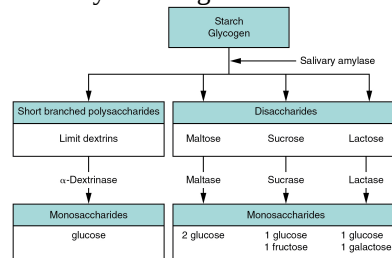
The average American diet is about 50 percent carbohydrates, which may be classified according to the number of monomers they contain of simple sugars (monosaccharides and disaccharides) and/or complex sugars (polysaccharides). Glucose, galactose, and fructose are the three monosaccharides that are commonly consumed and are readily absorbed. Your digestive system is also able to break down the disaccharide sucrose (regular table sugar: glucose + fructose), lactose (milk sugar: glucose + galactose), and maltose (grain sugar: glucose + glucose), and the polysaccharides glycogen and starch (chains of monosaccharides). Your bodies do not produce enzymes that can break down most fibrous polysaccharides, such as cellulose. While indigestible

polysaccharides do not provide any nutritional value, they do provide dietary fiber, which helps propel food through the alimentary canal.

The chemical digestion of starches begins in the mouth and has been reviewed above.

In the small intestine, **pancreatic amylase** does the ‘heavy lifting’ for starch and carbohydrate digestion ([link](#)). After amylases break down starch into smaller fragments, the brush border enzyme **α -dextrinase** starts working on **α -dextrin**, breaking off one glucose unit at a time. Three brush border enzymes hydrolyze sucrose, lactose, and maltose into monosaccharides. **Sucrase** splits sucrose into one molecule of fructose and one molecule of glucose; **maltase** breaks down maltose and maltotriose into two and three glucose molecules, respectively; and **lactase** breaks down lactose into one molecule of glucose and one molecule of galactose. Insufficient lactase can lead to lactose intolerance.

Carbohydrate Digestion Flow Chart



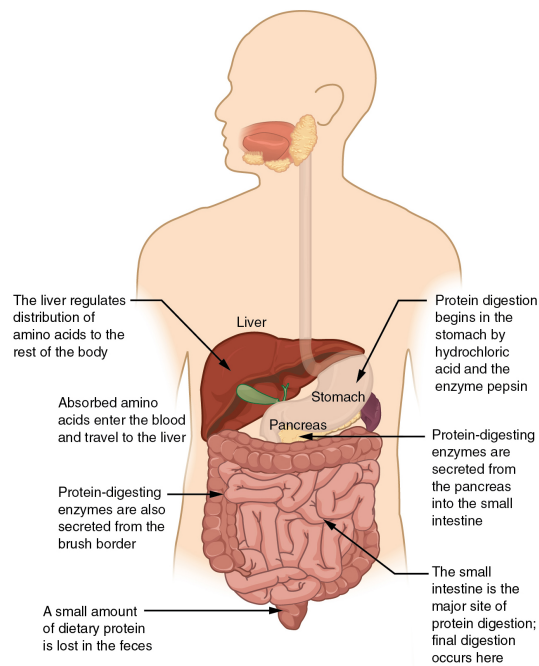
Carbohydrates are broken down into their monomers in a series of steps.

Protein Digestion

Proteins are polymers composed of amino acids linked by peptide bonds to form long chains. Digestion reduces them to their constituent amino acids. You usually consume about 15 to 20 percent of your total calorie intake as protein.

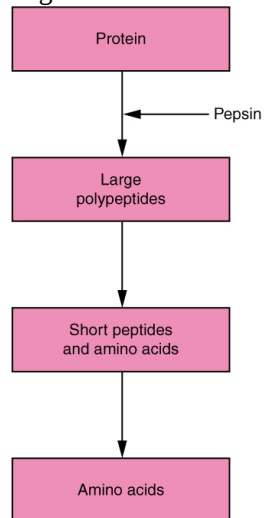
The digestion of protein starts in the stomach, where HCl and pepsin break proteins into smaller polypeptides, which then travel to the small intestine ([link](#)). Chemical digestion in the small intestine is continued by pancreatic enzymes, including chymotrypsin and trypsin, each of which act on specific bonds in amino acid sequences. At the same time, the cells of the brush border secrete enzymes such as **aminopeptidase** and **dipeptidase**, which further break down peptide chains. This results in molecules small enough to enter the bloodstream ([link](#)).

Digestion of Protein



The digestion of protein begins in the stomach and is completed in the small intestine.

Digestion of Protein Flow Chart



Proteins are successively broken down into their amino acid components.

Lipid Digestion

A healthy diet limits lipid intake to 35 percent of total calorie intake. The most common dietary lipids are triglycerides, which are made up of a glycerol molecule bound to three fatty acid chains. Small amounts of dietary cholesterol and phospholipids are also consumed.

The three lipases responsible for lipid digestion are lingual lipase, gastric lipase, and **pancreatic lipase**. However, because the pancreas is the only consequential source of lipase, virtually all lipid digestion occurs in the small intestine. Pancreatic lipase breaks down each triglyceride into two free fatty acids and a monoglyceride. The fatty acids include both short-chain (less than 10 to 12 carbons) and long-chain fatty acids.

Nucleic Acid Digestion

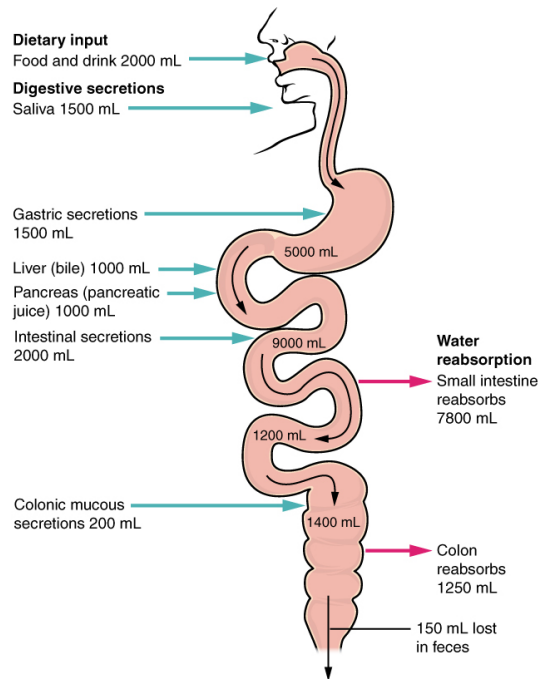
The nucleic acids DNA and RNA are found in most of the foods you eat. Two types of **pancreatic nuclease** are responsible for their digestion: **deoxyribonuclease**, which digests DNA, and **ribonuclease**, which digests RNA. The nucleotides produced by this digestion are further broken down by two intestinal brush border enzymes (**nucleosidase** and **phosphatase**) into pentoses, phosphates, and nitrogenous bases, which can be absorbed through the alimentary canal wall. The large food molecules that must be broken down into subunits are summarized [\[link\]](#)

| Absorbable Food Substances | |
|----------------------------|--|
| Source | Substance |
| Carbohydrates | Monosaccharides: glucose, galactose, and fructose |
| Proteins | Single amino acids, dipeptides, and tripeptides |
| Triglycerides | Monoacylglycerides, glycerol, and free fatty acids |
| Nucleic acids | Pentose sugars, phosphates, and nitrogenous bases |

Absorption

The mechanical and digestive processes have one goal: to convert food into molecules small enough to be absorbed by the epithelial cells of the intestinal villi. The absorptive capacity of the alimentary canal is almost endless. Each day, the alimentary canal processes up to 10 liters of food, liquids, and GI secretions, yet less than one liter enters the large intestine. Almost all ingested food, 80 percent of electrolytes, and 90 percent of water are absorbed in the small intestine. Although the entire small intestine is involved in the absorption of water and lipids, most absorption of carbohydrates and proteins occurs in the jejunum. Notably, bile salts and vitamin B₁₂ are absorbed in the terminal ileum. By the time chyme passes from the ileum into the large intestine, it is essentially indigestible food residue (mainly plant fibers like cellulose), some water, and millions of bacteria ([\[link\]](#)).

Digestive Secretions and Absorption of Water



Absorption is a complex process, in which nutrients from digested food are harvested.

Absorption can occur through five mechanisms: (1) active transport, (2) passive diffusion, (3) facilitated diffusion, (4) co-transport (or secondary active transport), and (5) endocytosis. As you will recall from Chapter 3, active transport refers to the movement of a substance across a cell membrane going from an area of lower concentration to an area of higher concentration (up the concentration gradient). In this type of transport, proteins within the cell membrane act as “pumps,” using cellular energy (ATP) to move the substance. Passive diffusion refers to the movement of substances from an area of higher concentration to an area of lower concentration, while facilitated diffusion refers to the movement of substances from an area of higher to an area of lower concentration using a carrier protein in the cell membrane. Co-transport uses the movement of one molecule through the membrane from higher to lower concentration to power the movement of another from lower to higher. Finally, endocytosis is a transportation process in which the cell membrane engulfs material. It requires energy, generally in the form of ATP.

Because the cell’s plasma membrane is made up of hydrophobic phospholipids, water-soluble nutrients must use transport molecules embedded in the membrane to enter cells. Moreover, substances cannot pass between the epithelial cells of the intestinal mucosa because these cells are bound together by tight junctions. Thus, substances can only enter blood capillaries by passing through the apical surfaces of epithelial cells and into the interstitial fluid. Water-soluble nutrients enter the capillary blood in the villi and travel to the liver via the hepatic portal vein.

In contrast to the water-soluble nutrients, lipid-soluble nutrients can diffuse through the plasma membrane. Once inside the cell, they are packaged for transport via the base of the cell and then enter the lacteals of the villi to be transported by lymphatic vessels to the systemic circulation via the thoracic duct. The absorption of most nutrients through the mucosa of the intestinal villi requires active transport fueled by ATP. The routes of absorption for each food category are summarized in [\[link\]](#).

| Absorption in the Alimentary Canal | | | | |
|---|---------------------------------|---|-----------------------------|---|
| Food | Breakdown products | Absorption mechanism | Entry to bloodstream | Destination |
| Carbohydrates | Glucose | Co-transport with sodium ions | Capillary blood in villi | Liver via hepatic portal vein |
| Carbohydrates | Galactose | Co-transport with sodium ions | Capillary blood in villi | Liver via hepatic portal vein |
| Carbohydrates | Fructose | Facilitated diffusion | Capillary blood in villi | Liver via hepatic portal vein |
| Protein | Amino acids | Co-transport with sodium ions | Capillary blood in villi | Liver via hepatic portal vein |
| Lipids | Long-chain fatty acids | Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons | Lacteals of villi | Systemic circulation via lymph entering thoracic duct |
| Lipids | Monoacylglycerides | Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons | Lacteals of villi | Systemic circulation via lymph entering thoracic duct |
| Lipids | Short-chain fatty acids | Simple diffusion | Capillary blood in villi | Liver via hepatic portal vein |
| Lipids | Glycerol | Simple diffusion | Capillary blood in villi | Liver via hepatic portal vein |
| Nucleic Acids | Nucleic acid digestion products | Active transport via membrane carriers | Capillary blood in villi | Liver via hepatic portal vein |

Carbohydrate Absorption

All carbohydrates are absorbed in the form of monosaccharides. The small intestine is highly efficient at this, absorbing monosaccharides at an estimated rate of 120 grams per hour. All normally digested dietary

carbohydrates are absorbed; indigestible fibers are eliminated in the feces. The monosaccharides glucose and galactose are transported into the epithelial cells by common protein carriers via secondary active transport (that is, co-transport with sodium ions). The monosaccharides leave these cells via facilitated diffusion and enter the capillaries through intercellular clefts. The monosaccharide fructose (which is in fruit) is absorbed and transported by facilitated diffusion alone. The monosaccharides combine with the transport proteins immediately after the disaccharides are broken down.

Protein Absorption

Active transport mechanisms, primarily in the duodenum and jejunum, absorb most proteins as their breakdown products, amino acids. Almost all (95 to 98 percent) protein is digested and absorbed in the small intestine. The type of carrier that transports an amino acid varies. Most carriers are linked to the active transport of sodium. Short chains of two amino acids (dipeptides) or three amino acids (tripeptides) are also transported actively. However, after they enter the absorptive epithelial cells, they are broken down into their amino acids before leaving the cell and entering the capillary blood via diffusion.

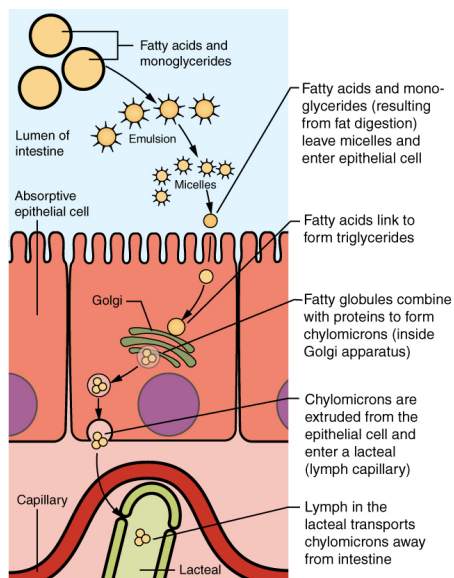
Lipid Absorption

About 95 percent of lipids are absorbed in the small intestine. Bile salts not only speed up lipid digestion, they are also essential to the absorption of the end products of lipid digestion. Short-chain fatty acids are relatively water soluble and can enter the absorptive cells (enterocytes) directly. The small size of short-chain fatty acids enables them to be absorbed by enterocytes via simple diffusion, and then take the same path as monosaccharides and amino acids into the blood capillary of a villus.

The large and hydrophobic long-chain fatty acids and monoacylglycerides are not so easily suspended in the watery intestinal chyme. However, bile salts and lecithin resolve this issue by enclosing them in a **micelle**, which is a tiny sphere with polar (hydrophilic) ends facing the watery environment and hydrophobic tails turned to the interior, creating a receptive environment for the long-chain fatty acids. The core also includes cholesterol and fat-soluble vitamins. Without micelles, lipids would sit on the surface of chyme and never come in contact with the absorptive surfaces of the epithelial cells. Micelles can easily squeeze between microvilli and get very near the luminal cell surface. At this point, lipid substances exit the micelle and are absorbed via simple diffusion.

The free fatty acids and monoacylglycerides that enter the epithelial cells are reincorporated into triglycerides. The triglycerides are mixed with phospholipids and cholesterol, and surrounded with a protein coat. This new complex, called a **chylomicron**, is a water-soluble lipoprotein. After being processed by the Golgi apparatus, chylomicrons are released from the cell ([link](#)). Too big to pass through the basement membranes of blood capillaries, chylomicrons instead enter the large pores of lacteals. The lacteals come together to form the lymphatic vessels. The chylomicrons are transported in the lymphatic vessels and empty through the thoracic duct into the subclavian vein of the circulatory system. Once in the bloodstream, the enzyme **lipoprotein lipase** breaks down the triglycerides of the chylomicrons into free fatty acids and glycerol. These breakdown products then pass through capillary walls to be used for energy by cells or stored in adipose tissue as fat. Liver cells combine the remaining chylomicron remnants with proteins, forming lipoproteins that transport cholesterol in the blood.

Lipid Absorption



Unlike amino acids and simple sugars, lipids are transformed as they are absorbed through epithelial cells.

Nucleic Acid Absorption

The products of nucleic acid digestion—pentose sugars, nitrogenous bases, and phosphate ions—are transported by carriers across the villus epithelium via active transport. These products then enter the bloodstream.

Mineral Absorption

The electrolytes absorbed by the small intestine are from both GI secretions and ingested foods. Since electrolytes dissociate into ions in water, most are absorbed via active transport throughout the entire small intestine. During absorption, co-transport mechanisms result in the accumulation of sodium ions inside the cells, whereas anti-port mechanisms reduce the potassium ion concentration inside the cells. To restore the sodium-potassium gradient across the cell membrane, a sodium-potassium pump requiring ATP pumps sodium out and potassium in.

In general, all minerals that enter the intestine are absorbed, whether you need them or not. Iron and calcium are exceptions; they are absorbed in the duodenum in amounts that meet the body's current requirements, as follows:

Iron—The ionic iron needed for the production of hemoglobin is absorbed into mucosal cells via active transport. Once inside mucosal cells, ionic iron binds to the protein ferritin, creating iron-ferritin complexes that store iron until needed. When the body has enough iron, most of the stored iron is lost when worn-out epithelial cells slough off. When the body needs iron because, for example, it is lost during acute or chronic bleeding, there is increased uptake of iron from the intestine and accelerated release of iron into the

bloodstream. Since women experience significant iron loss during menstruation, they have around four times as many iron transport proteins in their intestinal epithelial cells as do men.

Calcium—Blood levels of ionic calcium determine the absorption of dietary calcium. When blood levels of ionic calcium drop, parathyroid hormone (PTH) secreted by the parathyroid glands stimulates the release of calcium ions from bone matrices and increases the reabsorption of calcium by the kidneys. PTH also upregulates the activation of vitamin D in the kidney, which then facilitates intestinal calcium ion absorption.

Vitamin Absorption

The small intestine absorbs the vitamins that occur naturally in food and supplements. Fat-soluble vitamins (A, D, E, and K) are absorbed along with dietary lipids in micelles via simple diffusion. This is why you are advised to eat some fatty foods when you take fat-soluble vitamin supplements. Most water-soluble vitamins (including most B vitamins and vitamin C) also are absorbed by simple diffusion. An exception is vitamin B₁₂, which is a very large molecule. Intrinsic factor secreted in the stomach binds to vitamin B₁₂, preventing its digestion and creating a complex that binds to mucosal receptors in the terminal ileum, where it is taken up by endocytosis.

Water Absorption

Each day, about nine liters of fluid enter the small intestine. About 2.3 liters are ingested in foods and beverages, and the rest is from GI secretions. About 90 percent of this water is absorbed in the small intestine. Water absorption is driven by the concentration gradient of the water: The concentration of water is higher in chyme than it is in epithelial cells. Thus, water moves down its concentration gradient from the chyme into cells. As noted earlier, much of the remaining water is then absorbed in the colon.

Chapter Review

The small intestine is the site of most chemical digestion and almost all absorption. Chemical digestion breaks large food molecules down into their chemical building blocks, which can then be absorbed through the intestinal wall and into the general circulation. Intestinal brush border enzymes and pancreatic enzymes are responsible for the majority of chemical digestion. The breakdown of fat also requires bile.

Most nutrients are absorbed by transport mechanisms at the apical surface of enterocytes. Exceptions include lipids, fat-soluble vitamins, and most water-soluble vitamins. With the help of bile salts and lecithin, the dietary fats are emulsified to form micelles, which can carry the fat particles to the surface of the enterocytes. There, the micelles release their fats to diffuse across the cell membrane. The fats are then reassembled into triglycerides and mixed with other lipids and proteins into chylomicrons that can pass into lacteals. Other absorbed monomers travel from blood capillaries in the villus to the hepatic portal vein and then to the liver.

Review Questions

Exercise:

Problem: Where does the chemical digestion of starch begin?

- a. mouth
- b. esophagus
- c. stomach
- d. small intestine

Solution:

A

Exercise:

Problem: Which of these is involved in the chemical digestion of protein?

- a. pancreatic amylase
- b. trypsin
- c. sucrase
- d. pancreatic nuclease

Solution:

B

Exercise:

Problem: Where are most fat-digesting enzymes produced?

- a. small intestine
- b. gallbladder
- c. liver
- d. pancreas

Solution:

D

Exercise:

Problem: Which of these nutrients is absorbed mainly in the duodenum?

- a. glucose
- b. iron
- c. sodium
- d. water

Solution:

B

Critical Thinking Questions

Exercise:

Problem: Explain the role of bile salts and lecithin in the emulsification of lipids (fats).

Solution:

Bile salts and lecithin can emulsify large lipid globules because they are amphipathic; they have a nonpolar (hydrophobic) region that attaches to the large fat molecules as well as a polar (hydrophilic) region that interacts with the watery chyme in the intestine.

Exercise:

Problem:How is vitamin B₁₂ absorbed?

Solution:

Intrinsic factor secreted in the stomach binds to the large B₁₂ compound, creating a combination that can bind to mucosal receptors in the ileum.

Glossary

α -dextrin

breakdown product of starch

α -dextrinase

brush border enzyme that acts on α -dextrins

aminopeptidase

brush border enzyme that acts on proteins

chylomicron

large lipid-transport compound made up of triglycerides, phospholipids, cholesterol, and proteins

deoxyribonuclease

pancreatic enzyme that digests DNA

dipeptidase

brush border enzyme that acts on proteins

lactase

brush border enzyme that breaks down lactose into glucose and galactose

lipoprotein lipase

enzyme that breaks down triglycerides in chylomicrons into fatty acids and monoglycerides

maltase

brush border enzyme that breaks down maltose and maltotriose into two and three molecules of glucose, respectively

micelle

tiny lipid-transport compound composed of bile salts and phospholipids with a fatty acid and monoacylglyceride core

nucleosidase

brush border enzyme that digests nucleotides

pancreatic amylase

enzyme secreted by the pancreas that completes the chemical digestion of carbohydrates in the small intestine

pancreatic lipase

enzyme secreted by the pancreas that participates in lipid digestion

pancreatic nuclease

enzyme secreted by the pancreas that participates in nucleic acid digestion

phosphatase

brush border enzyme that digests nucleotides

ribonuclease

pancreatic enzyme that digests RNA

sucrase

brush border enzyme that breaks down sucrose into glucose and fructose

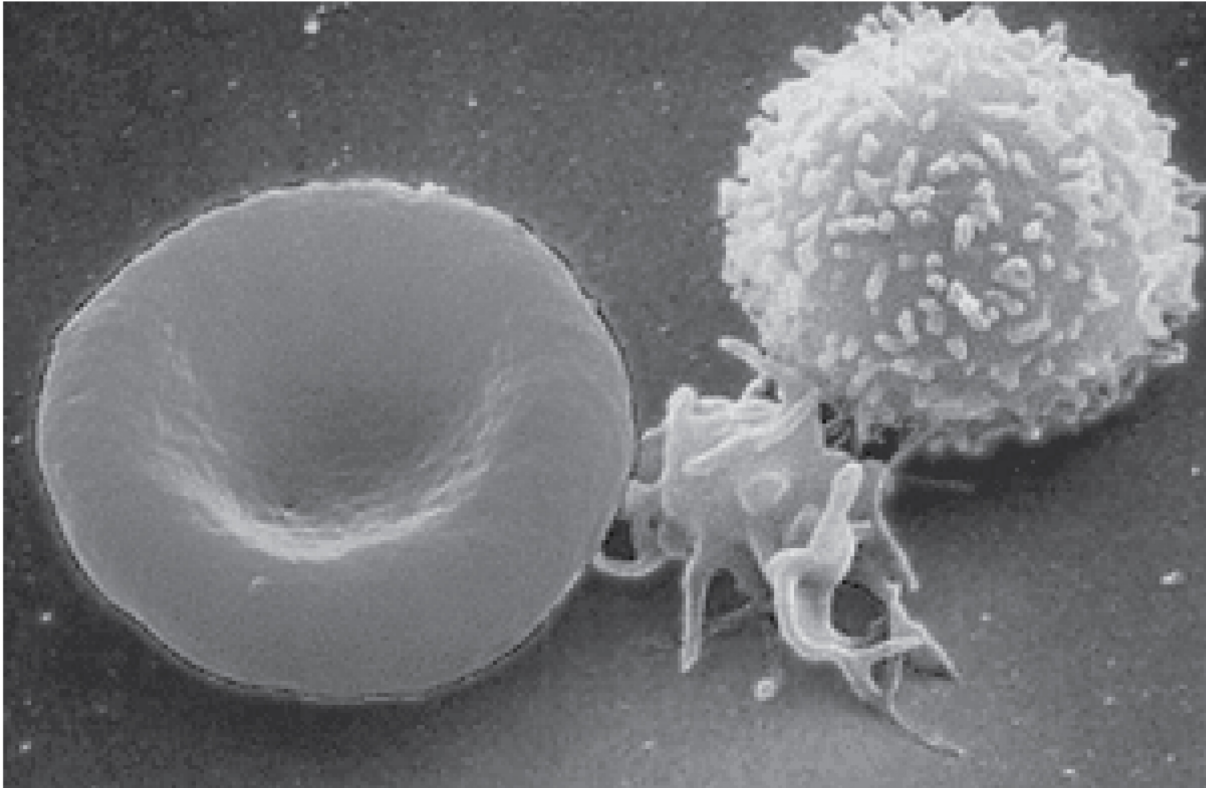
Introduction

class="introduction"

Blood Cells

A single
drop of
blood
contains
millions of
red blood
cells, white
blood cells,
and
platelets.
One of each
type is
shown here,
isolated
from a
scanning
electron
micrograph

.

**Note:****Chapter Objectives**

After studying this chapter, you will be able to:

- Identify the primary functions of blood, its fluid and cellular components, and its physical characteristics
- Identify the most important proteins and other solutes present in blood plasma
- Describe the formation of the formed element components of blood
- Discuss the structure and function of red blood cells and hemoglobin
- Classify and characterize white blood cells
- Describe the structure of platelets and explain the process of hemostasis
- Explain the significance of AB and Rh blood groups in blood transfusions
- Discuss a variety of blood disorders

Single-celled organisms do not need blood. They obtain nutrients directly from and excrete wastes directly into their environment. The human organism cannot do that. Our large, complex bodies need blood to deliver nutrients to and remove wastes from our trillions of cells. The heart pumps blood throughout the body in a network of blood vessels. Together, these three components—blood, heart, and vessels—makes up the cardiovascular system. This chapter focuses on the medium of transport: blood.

An Overview of Blood

By the end of this section, you will be able to:

- Identify the primary functions of blood in transportation, defense, and maintenance of homeostasis
- Name the fluid component of blood and the three major types of formed elements, and identify their relative proportions in a blood sample
- Discuss the unique physical characteristics of blood
- Identify the composition of blood plasma, including its most important solutes and plasma proteins

Recall that **blood** is a connective tissue. Like all connective tissues, it is made up of cellular elements and an extracellular matrix. The cellular elements—referred to as the **formed elements**—include **red blood cells (RBCs)**, **white blood cells (WBCs)**, and cell fragments called **platelets**. The extracellular matrix, called **plasma**, makes blood unique among connective tissues because it is fluid. This fluid, which is mostly water, perpetually suspends the formed elements and enables them to circulate throughout the body within the cardiovascular system.

Functions of Blood

The primary function of blood is to deliver oxygen and nutrients to and remove wastes from body cells, but that is only the beginning of the story. The specific functions of blood also include defense, distribution of heat, and maintenance of homeostasis.

Transportation

Nutrients from the foods you eat are absorbed in the digestive tract. Most of these travel in the bloodstream directly to the liver, where they are processed and released back into the bloodstream for delivery to body cells. Oxygen from the air you breathe diffuses into the blood, which moves from the lungs to the heart, which then pumps it out to the rest of the body. Moreover, endocrine glands scattered throughout the body release their

products, called hormones, into the bloodstream, which carries them to distant target cells. Blood also picks up cellular wastes and byproducts, and transports them to various organs for removal. For instance, blood moves carbon dioxide to the lungs for exhalation from the body, and various waste products are transported to the kidneys and liver for excretion from the body in the form of urine or bile.

Defense

Many types of WBCs protect the body from external threats, such as disease-causing bacteria that have entered the bloodstream in a wound. Other WBCs seek out and destroy internal threats, such as cells with mutated DNA that could multiply to become cancerous, or body cells infected with viruses.

When damage to the vessels results in bleeding, blood platelets and certain proteins dissolved in the plasma, the fluid portion of the blood, interact to block the ruptured areas of the blood vessels involved. This protects the body from further blood loss.

Maintenance of Homeostasis

Recall that body temperature is regulated via a classic negative-feedback loop. If you were exercising on a warm day, your rising core body temperature would trigger several homeostatic mechanisms, including increased transport of blood from your core to your body periphery, which is typically cooler. As blood passes through the vessels of the skin, heat would be dissipated to the environment, and the blood returning to your body core would be cooler. In contrast, on a cold day, blood is diverted away from the skin to maintain a warmer body core. In extreme cases, this may result in frostbite.

Blood also helps to maintain the chemical balance of the body. Proteins and other compounds in blood act as buffers, which thereby help to regulate the

pH of body tissues. Blood also helps to regulate the water content of body cells.

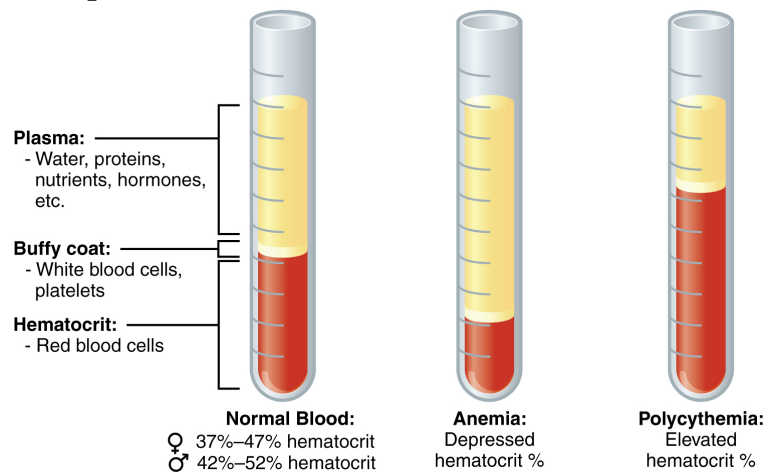
Composition of Blood

You have probably had blood drawn from a superficial vein in your arm, which was then sent to a lab for analysis. Some of the most common blood tests—for instance, those measuring lipid or glucose levels in plasma—determine which substances are present within blood and in what quantities. Other blood tests check for the composition of the blood itself, including the quantities and types of formed elements.

One such test, called a **hematocrit**, measures the percentage of RBCs, clinically known as erythrocytes, in a blood sample. It is performed by spinning the blood sample in a specialized centrifuge, a process that causes the heavier elements suspended within the blood sample to separate from the lightweight, liquid plasma ([\[link\]](#)). Because the heaviest elements in blood are the erythrocytes, these settle at the very bottom of the hematocrit tube. Located above the erythrocytes is a pale, thin layer composed of the remaining formed elements of blood. These are the WBCs, clinically known as leukocytes, and the platelets, cell fragments also called thrombocytes. This layer is referred to as the **buffy coat** because of its color; it normally constitutes less than 1 percent of a blood sample. Above the buffy coat is the blood plasma, normally a pale, straw-colored fluid, which constitutes the remainder of the sample.

The volume of erythrocytes after centrifugation is also commonly referred to as **packed cell volume (PCV)**. In normal blood, about 45 percent of a sample is erythrocytes. The hematocrit of any one sample can vary significantly, however, about 36–50 percent, according to gender and other factors. Normal hematocrit values for females range from 37 to 47, with a mean value of 41; for males, hematocrit ranges from 42 to 52, with a mean of 47. The percentage of other formed elements, the WBCs and platelets, is extremely small so it is not normally considered with the hematocrit. So the mean plasma percentage is the percent of blood that is not erythrocytes: for females, it is approximately 59 (or 100 minus 41), and for males, it is approximately 53 (or 100 minus 47).

Composition of Blood



The cellular elements of blood include a vast number of erythrocytes and comparatively fewer leukocytes and platelets. Plasma is the fluid in which the formed elements are suspended. A sample of blood spun in a centrifuge reveals that plasma is the lightest component. It floats at the top of the tube separated from the heaviest elements, the erythrocytes, by a buffy coat of leukocytes and platelets. Hematocrit is the percentage of the total sample that is comprised of erythrocytes. Depressed and elevated hematocrit levels are shown for comparison.

Characteristics of Blood

When you think about blood, the first characteristic that probably comes to mind is its color. Blood that has just taken up oxygen in the lungs is bright red, and blood that has released oxygen in the tissues is a more dusky red. This is because hemoglobin is a pigment that changes color, depending upon the degree of oxygen saturation.

Blood is viscous and somewhat sticky to the touch. It has a viscosity approximately five times greater than water. Viscosity is a measure of a fluid's thickness or resistance to flow, and is influenced by the presence of the plasma proteins and formed elements within the blood. The viscosity of blood has a dramatic impact on blood pressure and flow. Consider the difference in flow between water and honey. The more viscous honey would demonstrate a greater resistance to flow than the less viscous water. The same principle applies to blood.

The normal temperature of blood is slightly higher than normal body temperature—about 38 °C (or 100.4 °F), compared to 37 °C (or 98.6 °F) for an internal body temperature reading, although daily variations of 0.5 °C are normal. Although the surface of blood vessels is relatively smooth, as blood flows through them, it experiences some friction and resistance, especially as vessels age and lose their elasticity, thereby producing heat. This accounts for its slightly higher temperature.

The pH of blood averages about 7.4; however, it can range from 7.35 to 7.45 in a healthy person. Blood is therefore somewhat more basic (alkaline) on a chemical scale than pure water, which has a pH of 7.0. Blood contains numerous buffers that actually help to regulate pH.

Blood constitutes approximately 8 percent of adult body weight. Adult males typically average about 5 to 6 liters of blood. Females average 4–5 liters.

Blood Plasma

Like other fluids in the body, plasma is composed primarily of water: In fact, it is about 92 percent water. Dissolved or suspended within this water is a mixture of substances, most of which are proteins. There are literally hundreds of substances dissolved or suspended in the plasma, although many of them are found only in very small quantities.

Note:



Visit this [site](#) for a list of normal levels established for many of the substances found in a sample of blood. Serum, one of the specimen types included, refers to a sample of plasma after clotting factors have been removed. What types of measurements are given for levels of glucose in the blood?

Plasma Proteins

About 7 percent of the volume of plasma—nearly all that is not water—is made of proteins. These include several plasma proteins (proteins that are unique to the plasma), plus a much smaller number of regulatory proteins, including enzymes and some hormones. The major components of plasma are summarized in [\[link\]](#).

The three major groups of plasma proteins are as follows:

- **Albumin** is the most abundant of the plasma proteins. Manufactured by the liver, albumin molecules serve as binding proteins—transport vehicles for fatty acids and steroid hormones. Recall that lipids are hydrophobic; however, their binding to albumin enables their transport in the watery plasma. Albumin is also the most significant contributor to the osmotic pressure of blood; that is, its presence holds water inside the blood vessels and draws water from the tissues, across blood vessel walls, and into the bloodstream. This in turn helps to maintain both blood volume and blood pressure. Albumin normally accounts for approximately 54 percent of the total plasma protein content, in clinical levels of 3.5–5.0 g/dL blood.
- The second most common plasma proteins are the **globulins**. A heterogeneous group, there are three main subgroups known as alpha, beta, and gamma globulins. The alpha and beta globulins transport

iron, lipids, and the fat-soluble vitamins A, D, E, and K to the cells; like albumin, they also contribute to osmotic pressure. The gamma globulins are proteins involved in immunity and are better known as **antibodies** or **immunoglobulins**. Although other plasma proteins are produced by the liver, immunoglobulins are produced by specialized leukocytes known as plasma cells. (Seek additional content for more information about immunoglobulins.) Globulins make up approximately 38 percent of the total plasma protein volume, in clinical levels of 1.0–1.5 g/dL blood.

- The least abundant plasma protein is **fibrinogen**. Like albumin and the alpha and beta globulins, fibrinogen is produced by the liver. It is essential for blood clotting, a process described later in this chapter. Fibrinogen accounts for about 7 percent of the total plasma protein volume, in clinical levels of 0.2–0.45 g/dL blood.

Other Plasma Solutes

In addition to proteins, plasma contains a wide variety of other substances. These include various electrolytes, such as sodium, potassium, and calcium ions; dissolved gases, such as oxygen, carbon dioxide, and nitrogen; various organic nutrients, such as vitamins, lipids, glucose, and amino acids; and metabolic wastes. All of these nonprotein solutes combined contribute approximately 1 percent to the total volume of plasma.

Major Blood Components

| Component and % of blood | Subcomponent and % of component | Type and % (where appropriate) | Site of production | Major function(s) |
|----------------------------------|---|--|---|---|
| Plasma 46–63 percent | Water 92 percent | Fluid | Absorbed by intestinal tract or produced by metabolism | Transport medium |
| | Plasma proteins 7 percent | Albumin 54–60 percent | Liver | Maintain osmotic concentration, transport lipid molecules |
| | | Globulins 35–38 percent | Alpha globulins—liver | Transport, maintain osmotic concentration |
| | | | Beta globulins—liver | Transport, maintain osmotic concentration |
| | | | Gamma globulins (immunoglobulins)—plasma cells | Immune responses |
| | | Fibrinogen 4–7 percent | Liver | Blood clotting in hemostasis |
| | Regulatory proteins <1 percent | Hormones and enzymes | Various sources | Regulate various body functions |
| | Other solutes 1 percent | Nutrients, gases, and wastes | Absorbed by intestinal tract, exchanged in respiratory system, or produced by cells | Numerous and varied |
| Formed elements 37–54 percent | Erythrocytes 99 percent | Erythrocytes | Red bone marrow | Transport gases, primarily oxygen and some carbon dioxide |
| | Leukocytes <1 percent Platelets <1 percent | Granular leukocytes: neutrophils eosinophils basophils | Red bone marrow | Nonspecific immunity |
| | | Agranular leukocytes: lymphocytes monocytes | Lymphocytes: bone marrow and lymphatic tissue | Lymphocytes: specific immunity |
| | | | Monocytes: red bone marrow | Monocytes: nonspecific immunity |
| | Platelets <1 percent | | Megakaryocytes: red bone marrow | Hemostasis |

Note:

Career Connection

Phlebotomy and Medical Lab Technology

Phlebotomists are professionals trained to draw blood (phleb- = “a blood vessel”; -tomy = “to cut”). When more than a few drops of blood are

required, phlebotomists perform a venipuncture, typically of a surface vein in the arm. They perform a capillary stick on a finger, an earlobe, or the heel of an infant when only a small quantity of blood is required. An arterial stick is collected from an artery and used to analyze blood gases. After collection, the blood may be analyzed by medical laboratories or perhaps used for transfusions, donations, or research. While many allied health professionals practice phlebotomy, the American Society of Phlebotomy Technicians issues certificates to individuals passing a national examination, and some large labs and hospitals hire individuals expressly for their skill in phlebotomy.

Medical or clinical laboratories employ a variety of individuals in technical positions:

- Medical technologists (MT), also known as clinical laboratory technologists (CLT), typically hold a bachelor's degree and certification from an accredited training program. They perform a wide variety of tests on various body fluids, including blood. The information they provide is essential to the primary care providers in determining a diagnosis and in monitoring the course of a disease and response to treatment.
- Medical laboratory technicians (MLT) typically have an associate's degree but may perform duties similar to those of an MT.
- Medical laboratory assistants (MLA) spend the majority of their time processing samples and carrying out routine assignments within the lab. Clinical training is required, but a degree may not be essential to obtaining a position.

Chapter Review

Blood is a fluid connective tissue critical to the transportation of nutrients, gases, and wastes throughout the body; to defend the body against infection and other threats; and to the homeostatic regulation of pH, temperature, and other internal conditions. Blood is composed of formed elements—erythrocytes, leukocytes, and cell fragments called platelets—and a fluid extracellular matrix called plasma. More than 90 percent of plasma is water.

The remainder is mostly plasma proteins—mainly albumin, globulins, and fibrinogen—and other dissolved solutes such as glucose, lipids, electrolytes, and dissolved gases. Because of the formed elements and the plasma proteins and other solutes, blood is sticky and more viscous than water. It is also slightly alkaline, and its temperature is slightly higher than normal body temperature.

Interactive Link Questions

Exercise:

Problem:

Visit this [site](#) for a list of normal levels established for many of the substances found in a sample of blood. Serum, one of the specimen types included, refers to a sample of plasma after clotting factors have been removed. What types of measurements are given for levels of glucose in the blood?

Solution:

There are values given for percent saturation, tension, and blood gas, and there are listings for different types of hemoglobin.

Review Questions

Exercise:

Problem: Which of the following statements about blood is true?

- a. Blood is about 92 percent water.
- b. Blood is slightly more acidic than water.
- c. Blood is slightly more viscous than water.
- d. Blood is slightly more salty than seawater.

Solution:

C

Exercise:

Problem: Which of the following statements about albumin is true?

- a. It draws water out of the blood vessels and into the body's tissues.
- b. It is the most abundant plasma protein.
- c. It is produced by specialized leukocytes called plasma cells.
- d. All of the above are true.

Solution:

B

Exercise:

Problem:

Which of the following plasma proteins is *not* produced by the liver?

- a. fibrinogen
- b. alpha globulin
- c. beta globulin
- d. immunoglobulin

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

A patient's hematocrit is 42 percent. Approximately what percentage of the patient's blood is plasma?

Solution:

The patient's blood is approximately 58 percent plasma (since the buffy coat is less than 1 percent).

Exercise:**Problem:**

Why would it be incorrect to refer to the formed elements as cells?

Solution:

The formed elements include erythrocytes and leukocytes, which are cells (although mature erythrocytes do not have a nucleus); however, the formed elements also include platelets, which are not true cells but cell fragments.

Exercise:**Problem:**

True or false: The buffy coat is the portion of a blood sample that is made up of its proteins.

Solution:

False. The buffy coat is the portion of blood that is made up of its leukocytes and platelets.

Glossary

albumin

most abundant plasma protein, accounting for most of the osmotic pressure of plasma

antibodies

(also, immunoglobulins or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

blood

liquid connective tissue composed of formed elements—erythrocytes, leukocytes, and platelets—and a fluid extracellular matrix called plasma; component of the cardiovascular system

buffy coat

thin, pale layer of leukocytes and platelets that separates the erythrocytes from the plasma in a sample of centrifuged blood

fibrinogen

plasma protein produced in the liver and involved in blood clotting

formed elements

cellular components of blood; that is, erythrocytes, leukocytes, and platelets

globulins

heterogeneous group of plasma proteins that includes transport proteins, clotting factors, immune proteins, and others

hematocrit

(also, packed cell volume) volume percentage of erythrocytes in a sample of centrifuged blood

immunoglobulins

(also, antibodies or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

packed cell volume (PCV)

(also, hematocrit) volume percentage of erythrocytes present in a sample of centrifuged blood

plasma

in blood, the liquid extracellular matrix composed mostly of water that circulates the formed elements and dissolved materials throughout the cardiovascular system

platelets

(also, thrombocytes) one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

red blood cells (RBCs)

(also, erythrocytes) one of the formed elements of blood that transports oxygen

white blood cells (WBCs)

(also, leukocytes) one of the formed elements of blood that provides defense against disease agents and foreign materials

Production of the Formed Elements

By the end of this section, you will be able to:

- Trace the generation of the formed elements of blood from bone marrow stem cells
- Discuss the role of hemopoietic growth factors in promoting the production of the formed elements

The lifespan of the formed elements is very brief. Although one type of leukocyte called memory cells can survive for years, most erythrocytes, leukocytes, and platelets normally live only a few hours to a few weeks. Thus, the body must form new blood cells and platelets quickly and continuously. When you donate a unit of blood during a blood drive (approximately 475 mL, or about 1 pint), your body typically replaces the donated plasma within 24 hours, but it takes about 4 to 6 weeks to replace the blood cells. This restricts the frequency with which donors can contribute their blood. The process by which this replacement occurs is called **hemopoiesis**, or hematopoiesis (from the Greek root haima- = “blood”; -poiesis = “production”).

Sites of Hemopoiesis

Prior to birth, hemopoiesis occurs in a number of tissues, beginning with the yolk sac of the developing embryo, and continuing in the fetal liver, spleen, lymphatic tissue, and eventually the red bone marrow. Following birth, most hemopoiesis occurs in the red marrow, a connective tissue within the spaces of spongy (cancellous) bone tissue. In children, hemopoiesis can occur in the medullary cavity of long bones; in adults, the process is largely restricted to the cranial and pelvic bones, the vertebrae, the sternum, and the proximal epiphyses of the femur and humerus.

Throughout adulthood, the liver and spleen maintain their ability to generate the formed elements. This process is referred to as extramedullary hemopoiesis (meaning hemopoiesis outside the medullary cavity of adult bones). When a disease such as bone cancer destroys the bone marrow, causing hemopoiesis to fail, extramedullary hemopoiesis may be initiated.

Differentiation of Formed Elements from Stem Cells

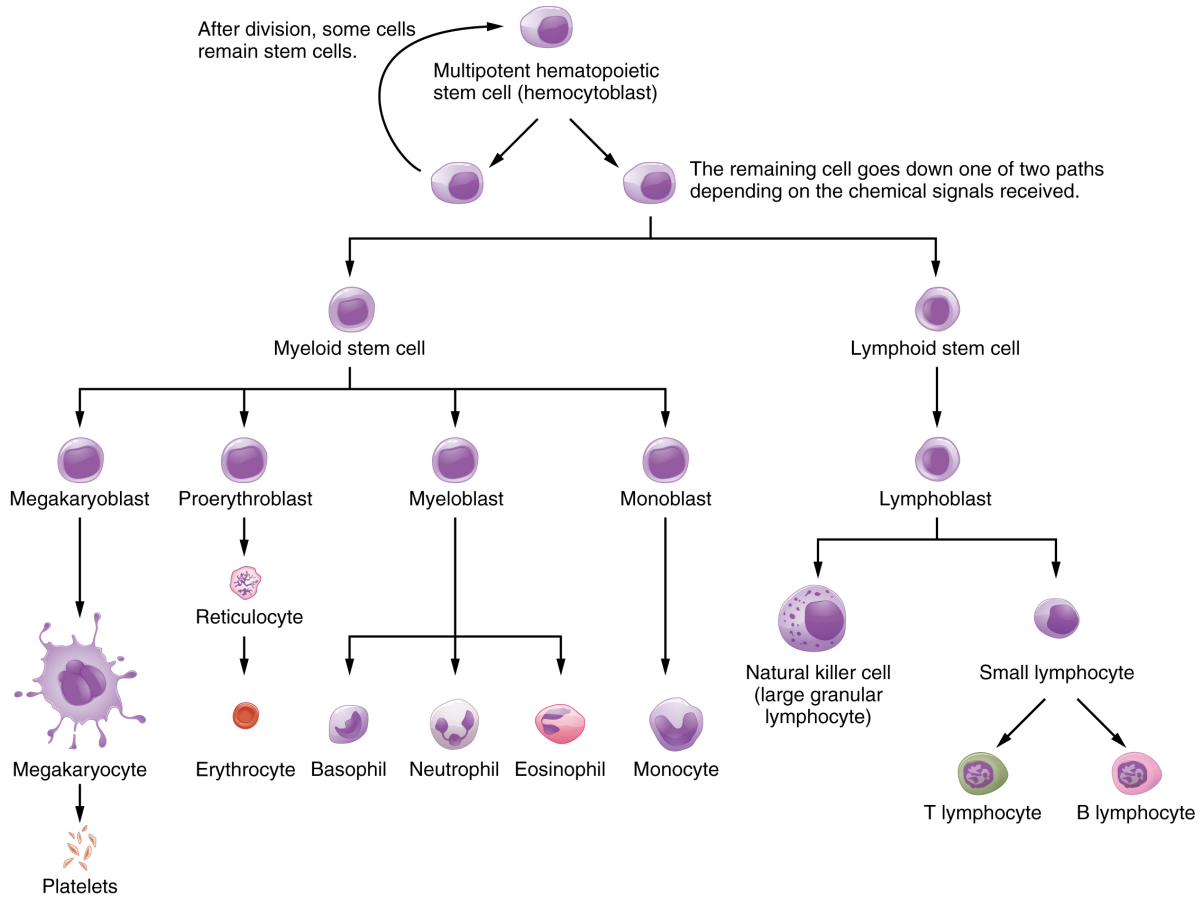
All formed elements arise from stem cells of the red bone marrow. Recall that stem cells undergo mitosis plus cytokinesis (cellular division) to give rise to new daughter cells: One of these remains a stem cell and the other differentiates into one of any number of diverse cell types. Stem cells may be viewed as occupying a hierarchical system, with some loss of the ability to diversify at each step. The **totipotent stem cell** is the zygote, or fertilized egg. The totipotent (toti- = “all”) stem cell gives rise to all cells of the human body. The next level is the **pluripotent stem cell**, which gives rise to multiple types of cells of the body and some of the supporting fetal membranes. Beneath this level, the mesenchymal cell is a stem cell that develops only into types of connective tissue, including fibrous connective tissue, bone, cartilage, and blood, but not epithelium, muscle, and nervous tissue. One step lower on the hierarchy of stem cells is the **hemopoietic stem cell**, or **hemocytoblast**. All of the formed elements of blood originate from this specific type of cell.

Hemopoiesis begins when the hemopoietic stem cell is exposed to appropriate chemical stimuli collectively called **hemopoietic growth factors**, which prompt it to divide and differentiate. One daughter cell remains a hemopoietic stem cell, allowing hemopoiesis to continue. The other daughter cell becomes either of two types of more specialized stem cells ([link](#)):

- **Lymphoid stem cells** give rise to a class of leukocytes known as lymphocytes, which include the various T cells, B cells, and natural killer (NK) cells, all of which function in immunity. However, hemopoiesis of lymphocytes progresses somewhat differently from the process for the other formed elements. In brief, lymphoid stem cells quickly migrate from the bone marrow to lymphatic tissues, including the lymph nodes, spleen, and thymus, where their production and differentiation continues. B cells are so named since they mature in the bone marrow, while T cells mature in the thymus.
- **Myeloid stem cells** give rise to all the other formed elements, including the erythrocytes; megakaryocytes that produce platelets; and

a myeloblast lineage that gives rise to monocytes and three forms of granular leukocytes: neutrophils, eosinophils, and basophils.

Hematopoietic System of Bone Marrow



Hemopoiesis is the proliferation and differentiation of the formed elements of blood.

Lymphoid and myeloid stem cells do not immediately divide and differentiate into mature formed elements. As you can see in [\[link\]](#), there are several intermediate stages of precursor cells (literally, forerunner cells), many of which can be recognized by their names, which have the suffix -blast. For instance, megakaryoblasts are the precursors of megakaryocytes, and proerythroblasts become reticulocytes, which eject their nucleus and most other organelles before maturing into erythrocytes.

Hemopoietic Growth Factors

Development from stem cells to precursor cells to mature cells is again initiated by hemopoietic growth factors. These include the following:

- **Erythropoietin (EPO)** is a glycoprotein hormone secreted by the interstitial fibroblast cells of the kidneys in response to low oxygen levels. It prompts the production of erythrocytes. Some athletes use synthetic EPO as a performance-enhancing drug (called blood doping) to increase RBC counts and subsequently increase oxygen delivery to tissues throughout the body. EPO is a banned substance in most organized sports, but it is also used medically in the treatment of certain anemia, specifically those triggered by certain types of cancer, and other disorders in which increased erythrocyte counts and oxygen levels are desirable.
- **Thrombopoietin**, another glycoprotein hormone, is produced by the liver and kidneys. It triggers the development of megakaryocytes into platelets.
- **Cytokines** are glycoproteins secreted by a wide variety of cells, including red bone marrow, leukocytes, macrophages, fibroblasts, and endothelial cells. They act locally as autocrine or paracrine factors, stimulating the proliferation of progenitor cells and helping to stimulate both nonspecific and specific resistance to disease. There are two major subtypes of cytokines known as colony-stimulating factors and interleukins.
 - **Colony-stimulating factors (CSFs)** are glycoproteins that act locally, as autocrine or paracrine factors. Some trigger the differentiation of myeloblasts into granular leukocytes, namely, neutrophils, eosinophils, and basophils. These are referred to as granulocyte CSFs. A different CSF induces the production of monocytes, called monocyte CSFs. Both granulocytes and monocytes are stimulated by GM-CSF; granulocytes, monocytes, platelets, and erythrocytes are stimulated by multi-CSF. Synthetic forms of these hormones are often administered to patients with various forms of cancer who are receiving chemotherapy to revive their WBC counts.

- **Interleukins** are another class of cytokine signaling molecules important in hemopoiesis. They were initially thought to be secreted uniquely by leukocytes and to communicate only with other leukocytes, and were named accordingly, but are now known to be produced by a variety of cells including bone marrow and endothelium. Researchers now suspect that interleukins may play other roles in body functioning, including differentiation and maturation of cells, producing immunity and inflammation. To date, more than a dozen interleukins have been identified, with others likely to follow. They are generally numbered IL-1, IL-2, IL-3, etc.

Note:**Everyday Connection****Blood Doping**

In its original intent, the term blood doping was used to describe the practice of injecting by transfusion supplemental RBCs into an individual, typically to enhance performance in a sport. Additional RBCs would deliver more oxygen to the tissues, providing extra aerobic capacity, clinically referred to as VO_2 max. The source of the cells was either from the recipient (autologous) or from a donor with compatible blood (homologous). This practice was aided by the well-developed techniques of harvesting, concentrating, and freezing of the RBCs that could be later thawed and injected, yet still retain their functionality. These practices are considered illegal in virtually all sports and run the risk of infection, significantly increasing the viscosity of the blood and the potential for transmission of blood-borne pathogens if the blood was collected from another individual.

With the development of synthetic EPO in the 1980s, it became possible to provide additional RBCs by artificially stimulating RBC production in the bone marrow. Originally developed to treat patients suffering from anemia, renal failure, or cancer treatment, large quantities of EPO can be generated by recombinant DNA technology. Synthetic EPO is injected under the skin and can increase hematocrit for many weeks. It may also induce polycythemia and raise hematocrit to 70 or greater. This increased

viscosity raises the resistance of the blood and forces the heart to pump more powerfully; in extreme cases, it has resulted in death. Other drugs such as cobalt II chloride have been shown to increase natural EPO gene expression. Blood doping has become problematic in many sports, especially cycling. Lance Armstrong, winner of seven Tour de France and many other cycling titles, was stripped of his victories and admitted to blood doping in 2013.

Note:



Watch this [video](#) to see doctors discuss the dangers of blood doping in sports. What are the some potential side effects of blood doping?

Bone Marrow Sampling and Transplants

Sometimes, a healthcare provider will order a **bone marrow biopsy**, a diagnostic test of a sample of red bone marrow, or a **bone marrow transplant**, a treatment in which a donor's healthy bone marrow—and its stem cells—replaces the faulty bone marrow of a patient. These tests and procedures are often used to assist in the diagnosis and treatment of various severe forms of anemia, such as thalassemia major and sickle cell anemia, as well as some types of cancer, specifically leukemia.

In the past, when a bone marrow sample or transplant was necessary, the procedure would have required inserting a large-bore needle into the region near the iliac crest of the pelvic bones (os coxae). This location was preferred, since its location close to the body surface makes it more

accessible, and it is relatively isolated from most vital organs. Unfortunately, the procedure is quite painful.

Now, direct sampling of bone marrow can often be avoided. In many cases, stem cells can be isolated in just a few hours from a sample of a patient's blood. The isolated stem cells are then grown in culture using the appropriate hemopoietic growth factors, and analyzed or sometimes frozen for later use.

For an individual requiring a transplant, a matching donor is essential to prevent the immune system from destroying the donor cells—a phenomenon known as tissue rejection. To treat patients with bone marrow transplants, it is first necessary to destroy the patient's own diseased marrow through radiation and/or chemotherapy. Donor bone marrow stem cells are then intravenously infused. From the bloodstream, they establish themselves in the recipient's bone marrow.

Chapter Review

Through the process of hemopoiesis, the formed elements of blood are continually produced, replacing the relatively short-lived erythrocytes, leukocytes, and platelets. Hemopoiesis begins in the red bone marrow, with hemopoietic stem cells that differentiate into myeloid and lymphoid lineages. Myeloid stem cells give rise to most of the formed elements. Lymphoid stem cells give rise only to the various lymphocytes designated as B and T cells, and NK cells. Hemopoietic growth factors, including erythropoietin, thrombopoietin, colony-stimulating factors, and interleukins, promote the proliferation and differentiation of formed elements.

Interactive Link Questions

Exercise:

Problem:

Watch this [video](#) to see doctors discuss the dangers of blood doping in sports. What are the some potential side effects of blood doping?

Solution:

Side effects can include heart disease, stroke, pulmonary embolism, and virus transmission.

Review Questions**Exercise:****Problem:**

Which of the formed elements arise from myeloid stem cells?

- a. B cells
- b. natural killer cells
- c. platelets
- d. all of the above

Solution:

C

Exercise:**Problem:**

Which of the following statements about erythropoietin is true?

- a. It facilitates the proliferation and differentiation of the erythrocyte lineage.
- b. It is a hormone produced by the thyroid gland.
- c. It is a hemopoietic growth factor that prompts lymphoid stem cells to leave the bone marrow.
- d. Both a and b are true.

Solution:

A

Exercise:

Problem:

Interleukins are associated primarily with which of the following?

- a. production of various lymphocytes
- b. immune responses
- c. inflammation
- d. all of the above

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

Myelofibrosis is a disorder in which inflammation and scar tissue formation in the bone marrow impair hemopoiesis. One sign is an enlarged spleen. Why?

Solution:

When disease impairs the ability of the bone marrow to participate in hemopoiesis, extramedullary hemopoiesis begins in the patient's liver and spleen. This causes the spleen to enlarge.

Exercise:

Problem:

Would you expect a patient with a form of cancer called acute myelogenous leukemia to experience impaired production of erythrocytes, or impaired production of lymphocytes? Explain your choice.

Solution:

The adjective myelogenous suggests a condition originating from (generated by) myeloid cells. Acute myelogenous leukemia impairs the production of erythrocytes and other mature formed elements of the myeloid stem cell lineage. Lymphocytes arise from the lymphoid stem cell line.

Glossary

bone marrow biopsy

diagnostic test of a sample of red bone marrow

bone marrow transplant

treatment in which a donor's healthy bone marrow with its stem cells replaces diseased or damaged bone marrow of a patient

colony-stimulating factors (CSFs)

glycoproteins that trigger the proliferation and differentiation of myeloblasts into granular leukocytes (basophils, neutrophils, and eosinophils)

cytokines

class of proteins that act as autocrine or paracrine signaling molecules; in the cardiovascular system, they stimulate the proliferation of progenitor cells and help to stimulate both nonspecific and specific resistance to disease

erythropoietin (EPO)

glycoprotein that triggers the bone marrow to produce RBCs; secreted by the kidney in response to low oxygen levels

hemocytoblast

hemopoietic stem cell that gives rise to the formed elements of blood

hemopoiesis

production of the formed elements of blood

hemopoietic growth factors

chemical signals including erythropoietin, thrombopoietin, colony-stimulating factors, and interleukins that regulate the differentiation and proliferation of particular blood progenitor cells

hemopoietic stem cell

type of pluripotent stem cell that gives rise to the formed elements of blood (hemocytoblast)

interleukins

signaling molecules that may function in hemopoiesis, inflammation, and specific immune responses

lymphoid stem cells

type of hemopoietic stem cells that gives rise to lymphocytes, including various T cells, B cells, and NK cells, all of which function in immunity

myeloid stem cells

type of hemopoietic stem cell that gives rise to some formed elements, including erythrocytes, megakaryocytes that produce platelets, and a myeloblast lineage that gives rise to monocytes and three forms of granular leukocytes (neutrophils, eosinophils, and basophils)

pluripotent stem cell

stem cell that derives from totipotent stem cells and is capable of differentiating into many, but not all, cell types

totipotent stem cell

embryonic stem cell that is capable of differentiating into any and all cells of the body; enabling the full development of an organism

thrombopoietin

hormone secreted by the liver and kidneys that prompts the development of megakaryocytes into thrombocytes (platelets)




Erythrocytes

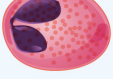
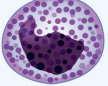



By the end of this section, you will be able to:

- Describe the anatomy of erythrocytes
- Discuss the various steps in the lifecycle of an erythrocyte
- Explain the composition and function of hemoglobin

The **erythrocyte**, commonly known as a red blood cell (or RBC), is by far the most common formed element: A single drop of blood contains millions of erythrocytes and just thousands of leukocytes. Specifically, males have about 5.4 million erythrocytes per microliter (μL) of blood, and females have approximately 4.8 million per μL . In fact, erythrocytes are estimated to make up about 25 percent of the total cells in the body. As you can imagine, they are quite small cells, with a mean diameter of only about 7–8 micrometers (μm) ([link](#)). The primary functions of erythrocytes are to pick up inhaled oxygen from the lungs and transport it to the body's tissues, and to pick up some (about 24 percent) carbon dioxide waste at the tissues and transport it to the lungs for exhalation. Erythrocytes remain within the vascular network. Although leukocytes typically leave the blood vessels to perform their defensive functions, movement of erythrocytes from the blood vessels is abnormal.

Summary of Formed Elements in Blood

| Formed element | Major subtypes | Numbers present per microliter (μL) and mean (range) | Appearance in a standard blood smear | Summary of functions | Comments |
|---|---|---|---|--|---|
| Erythrocytes (red blood cells)  | | 5.2 million (4.4–6.0 million) | Flattened biconcave disk; no nucleus; pale red color | Transport oxygen and some carbon dioxide between tissues and lungs | Lifespan of approximately 120 days |
| Leukocytes (white blood cells) | | 7000 (5000–10,000) | Obvious dark-staining nucleus | All function in body defenses | Exit capillaries and move into tissues; lifespan of usually a few hours or days |
| | Granulocytes including neutrophils, eosinophils, and basophils | 4360 (1800–9950) | Abundant granules in cytoplasm; nucleus normally lobed | Nonspecific (innate) resistance to disease | Classified according to membrane-bound granules in cytoplasm |
| | Neutrophils  | 4150 (1800–7300) | Nuclear lobes increase with age; pale lilac granules | Phagocytic; particularly effective against bacteria. Release cytotoxic chemicals from granules | Most common leukocyte; lifespan of minutes to days |
| | Eosinophils  | 165 (0–700) | Nucleus generally two-lobed; bright red-orange granules | Phagocytic cells; particularly effective with antigen-antibody | Lifespan of minutes to days |

| | | | | | |
|--|--|------------------------------|---|---|--|
| |  | | | complexes. Release antihistamines. Increase in allergies and parasitic infections | |
| |  Basophils | 44 (0–150) | Nucleus generally two-lobed but difficult to see due to presence of heavy, dense, dark purple granules | Promotes inflammation | Least common leukocyte; lifespan unknown |
| | Agranulocytes including lymphocytes and monocytes | 2640 (1700–4950) | Lack abundant granules in cytoplasm; have a simple-shaped nucleus that may be indented | Body defenses | Group consists of two major cell types from different lineages |
| |  Lymphocytes | 2185 (1500–4000) | Spherical cells with a single often large nucleus occupying much of the cell's volume; stains purple; seen in large (natural killer cells) and small (B and T cells) variants | Primarily specific (adaptive) immunity: T cells directly attack other cells (cellular immunity); B cells release antibodies (humoral immunity); natural killer cells are similar to T cells but nonspecific | Initial cells originate in bone marrow, but secondary production occurs in lymphatic tissue; several distinct subtypes; memory cells form after exposure to a pathogen and rapidly increase responses to subsequent exposure; lifespan of many years |
| |  Monocytes | 455 (200–950) | Largest leukocyte with an indented or horseshoe-shaped nucleus | Very effective phagocytic cells engulfing pathogens or worn out cells; also serve as antigen-presenting cells (APCs) for other components of the immune system | Produced in red bone marrow; referred to as macrophages after leaving circulation |
| Platelets  | | 350,000 (150,000–500,000) | Cellular fragments surrounded by a plasma membrane and containing granules; purple stain | Hemostasis plus release growth factors for repair and healing of tissue | Formed from megakaryocytes that remain in the red bone marrow and shed platelets into circulation |

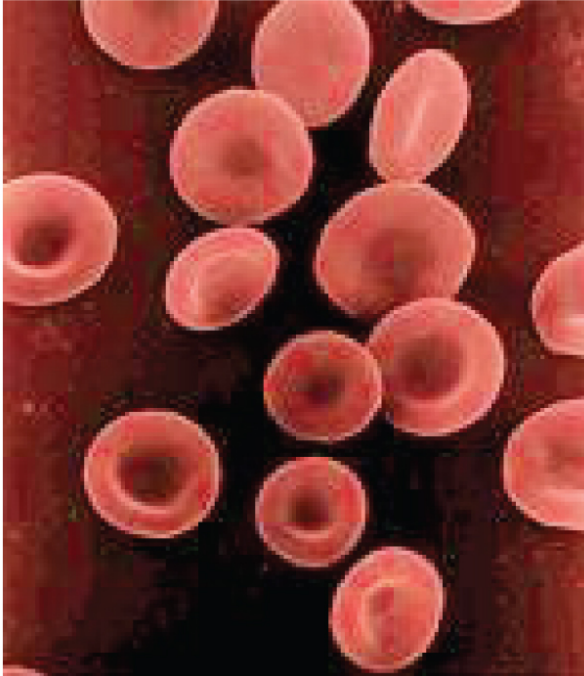
Shape and Structure of Erythrocytes

As an erythrocyte matures in the red bone marrow, it extrudes its nucleus and most of its other organelles. During the first day or two that it is in the circulation, an immature erythrocyte, known as a **reticulocyte**, will still typically contain remnants of organelles. Reticulocytes should comprise approximately 1–2 percent of the erythrocyte count and provide a rough estimate of the rate of RBC production, with abnormally low or high rates indicating deviations in the production of these cells. These remnants, primarily of networks (reticulum) of ribosomes, are quickly shed, however, and mature, circulating erythrocytes have few internal cellular structural components. Lacking mitochondria, for example, they rely on anaerobic respiration. This means that they do not utilize any of the oxygen they are transporting, so they can deliver it all to the tissues. They also lack

endoplasmic reticula and do not synthesize proteins. Erythrocytes do, however, contain some structural proteins that help the blood cells maintain their unique structure and enable them to change their shape to squeeze through capillaries. This includes the protein spectrin, a cytoskeletal protein element.

Erythrocytes are biconcave disks; that is, they are plump at their periphery and very thin in the center ([\[link\]](#)). Since they lack most organelles, there is more interior space for the presence of the hemoglobin molecules that, as you will see shortly, transport gases. The biconcave shape also provides a greater surface area across which gas exchange can occur, relative to its volume; a sphere of a similar diameter would have a lower surface area-to-volume ratio. In the capillaries, the oxygen carried by the erythrocytes can diffuse into the plasma and then through the capillary walls to reach the cells, whereas some of the carbon dioxide produced by the cells as a waste product diffuses into the capillaries to be picked up by the erythrocytes. Capillary beds are extremely narrow, slowing the passage of the erythrocytes and providing an extended opportunity for gas exchange to occur. However, the space within capillaries can be so minute that, despite their own small size, erythrocytes may have to fold in on themselves if they are to make their way through. Fortunately, their structural proteins like spectrin are flexible, allowing them to bend over themselves to a surprising degree, then spring back again when they enter a wider vessel. In wider vessels, erythrocytes may stack up much like a roll of coins, forming a rouleaux, from the French word for “roll.”

Shape of Red Blood Cells

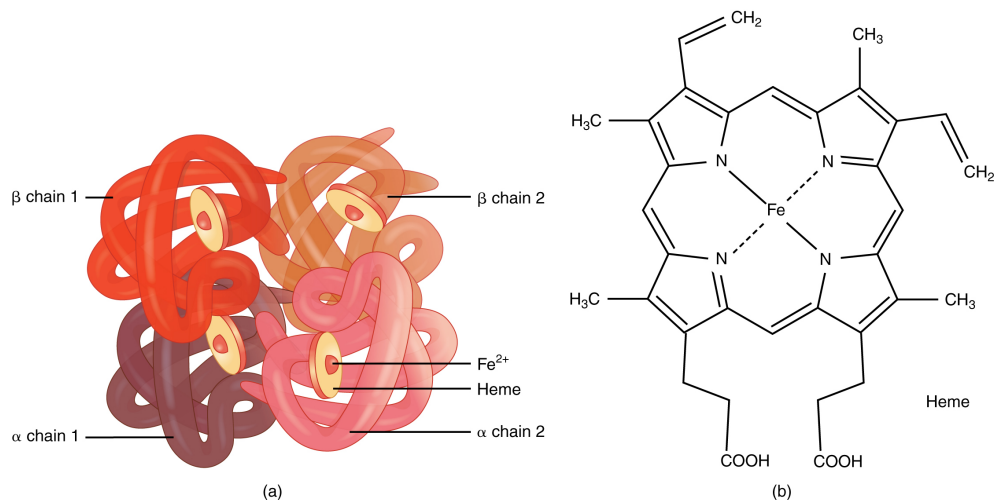


Erythrocytes are biconcave discs with very shallow centers. This shape optimizes the ratio of surface area to volume, facilitating gas exchange. It also enables them to fold up as they move through narrow blood vessels.

Hemoglobin

Hemoglobin is a large molecule made up of proteins and iron. It consists of four folded chains of a protein called **globin**, designated alpha 1 and 2, and beta 1 and 2 ([link](#)**a**). Each of these globin molecules is bound to a red pigment molecule called **heme**, which contains an ion of iron (Fe^{2+}) ([link](#)**b**).

Hemoglobin



(a) A molecule of hemoglobin contains four globin proteins, each of which is bound to one molecule of the iron-containing pigment heme. (b) A single erythrocyte can contain 300 million hemoglobin molecules, and thus more than 1 billion oxygen molecules.

Each iron ion in the heme can bind to one oxygen molecule; therefore, each hemoglobin molecule can transport four oxygen molecules. An individual erythrocyte may contain about 300 million hemoglobin molecules, and therefore can bind to and transport up to 1.2 billion oxygen molecules (see [\[link\]](#)b).

In the lungs, hemoglobin picks up oxygen, which binds to the iron ions, forming **oxyhemoglobin**. The bright red, oxygenated hemoglobin travels to the body tissues, where it releases some of the oxygen molecules, becoming darker red **deoxyhemoglobin**, sometimes referred to as reduced hemoglobin. Oxygen release depends on the need for oxygen in the surrounding tissues, so hemoglobin rarely if ever leaves all of its oxygen behind. In the capillaries, carbon dioxide enters the bloodstream. About 76 percent dissolves in the plasma, some of it remaining as dissolved CO_2 , and the remainder forming bicarbonate ion. About 23–24 percent of it binds to the amino acids in hemoglobin, forming a molecule known as **carbaminohemoglobin**. From the capillaries, the hemoglobin carries

carbon dioxide back to the lungs, where it releases it for exchange of oxygen.

Changes in the levels of RBCs can have significant effects on the body's ability to effectively deliver oxygen to the tissues. Ineffective hematopoiesis results in insufficient numbers of RBCs and results in one of several forms of anemia. An overproduction of RBCs produces a condition called polycythemia. The primary drawback with polycythemia is not a failure to directly deliver enough oxygen to the tissues, but rather the increased viscosity of the blood, which makes it more difficult for the heart to circulate the blood.

In patients with insufficient hemoglobin, the tissues may not receive sufficient oxygen, resulting in another form of anemia. In determining oxygenation of tissues, the value of greatest interest in healthcare is the percent saturation; that is, the percentage of hemoglobin sites occupied by oxygen in a patient's blood. Clinically this value is commonly referred to simply as "percent sat."

Percent saturation is normally monitored using a device known as a pulse oximeter, which is applied to a thin part of the body, typically the tip of the patient's finger. The device works by sending two different wavelengths of light (one red, the other infrared) through the finger and measuring the light with a photodetector as it exits. Hemoglobin absorbs light differentially depending upon its saturation with oxygen. The machine calibrates the amount of light received by the photodetector against the amount absorbed by the partially oxygenated hemoglobin and presents the data as percent saturation. Normal pulse oximeter readings range from 95–100 percent. Lower percentages reflect **hypoxemia**, or low blood oxygen. The term hypoxia is more generic and simply refers to low oxygen levels. Oxygen levels are also directly monitored from free oxygen in the plasma typically following an arterial stick. When this method is applied, the amount of oxygen present is expressed in terms of partial pressure of oxygen or simply pO_2 and is typically recorded in units of millimeters of mercury, mm Hg.

The kidneys filter about 180 liters (~380 pints) of blood in an average adult each day, or about 20 percent of the total resting volume, and thus serve as ideal sites for receptors that determine oxygen saturation. In response to

hypoxemia, less oxygen will exit the vessels supplying the kidney, resulting in hypoxia (low oxygen concentration) in the tissue fluid of the kidney where oxygen concentration is actually monitored. Interstitial fibroblasts within the kidney secrete EPO, thereby increasing erythrocyte production and restoring oxygen levels. In a classic negative-feedback loop, as oxygen saturation rises, EPO secretion falls, and vice versa, thereby maintaining homeostasis. Populations dwelling at high elevations, with inherently lower levels of oxygen in the atmosphere, naturally maintain a hematocrit higher than people living at sea level. Consequently, people traveling to high elevations may experience symptoms of hypoxemia, such as fatigue, headache, and shortness of breath, for a few days after their arrival. In response to the hypoxemia, the kidneys secrete EPO to step up the production of erythrocytes until homeostasis is achieved once again. To avoid the symptoms of hypoxemia, or altitude sickness, mountain climbers typically rest for several days to a week or more at a series of camps situated at increasing elevations to allow EPO levels and, consequently, erythrocyte counts to rise. When climbing the tallest peaks, such as Mt. Everest and K2 in the Himalayas, many mountain climbers rely upon bottled oxygen as they near the summit.

Lifecycle of Erythrocytes

Production of erythrocytes in the marrow occurs at the staggering rate of more than 2 million cells per second. For this production to occur, a number of raw materials must be present in adequate amounts. These include the same nutrients that are essential to the production and maintenance of any cell, such as glucose, lipids, and amino acids. However, erythrocyte production also requires several trace elements:

- **Iron.** We have said that each heme group in a hemoglobin molecule contains an ion of the trace mineral iron. On average, less than 20 percent of the iron we consume is absorbed. Heme iron, from animal foods such as meat, poultry, and fish, is absorbed more efficiently than non-heme iron from plant foods. Upon absorption, iron becomes part of the body's total iron pool. The bone marrow, liver, and spleen can store iron in the protein compounds **ferritin** and **hemosiderin**. Ferroportin transports the iron across the intestinal cell plasma

membranes and from its storage sites into tissue fluid where it enters the blood. When EPO stimulates the production of erythrocytes, iron is released from storage, bound to transferrin, and carried to the red marrow where it attaches to erythrocyte precursors.

- Copper. A trace mineral, copper is a component of two plasma proteins, hephaestin and ceruloplasmin. Without these, hemoglobin could not be adequately produced. Located in intestinal villi, hephaestin enables iron to be absorbed by intestinal cells. Ceruloplasmin transports copper. Both enable the oxidation of iron from Fe^{2+} to Fe^{3+} , a form in which it can be bound to its transport protein, **transferrin**, for transport to body cells. In a state of copper deficiency, the transport of iron for heme synthesis decreases, and iron can accumulate in tissues, where it can eventually lead to organ damage.
- Zinc. The trace mineral zinc functions as a co-enzyme that facilitates the synthesis of the heme portion of hemoglobin.
- B vitamins. The B vitamins folate and vitamin B₁₂ function as co-enzymes that facilitate DNA synthesis. Thus, both are critical for the synthesis of new cells, including erythrocytes.

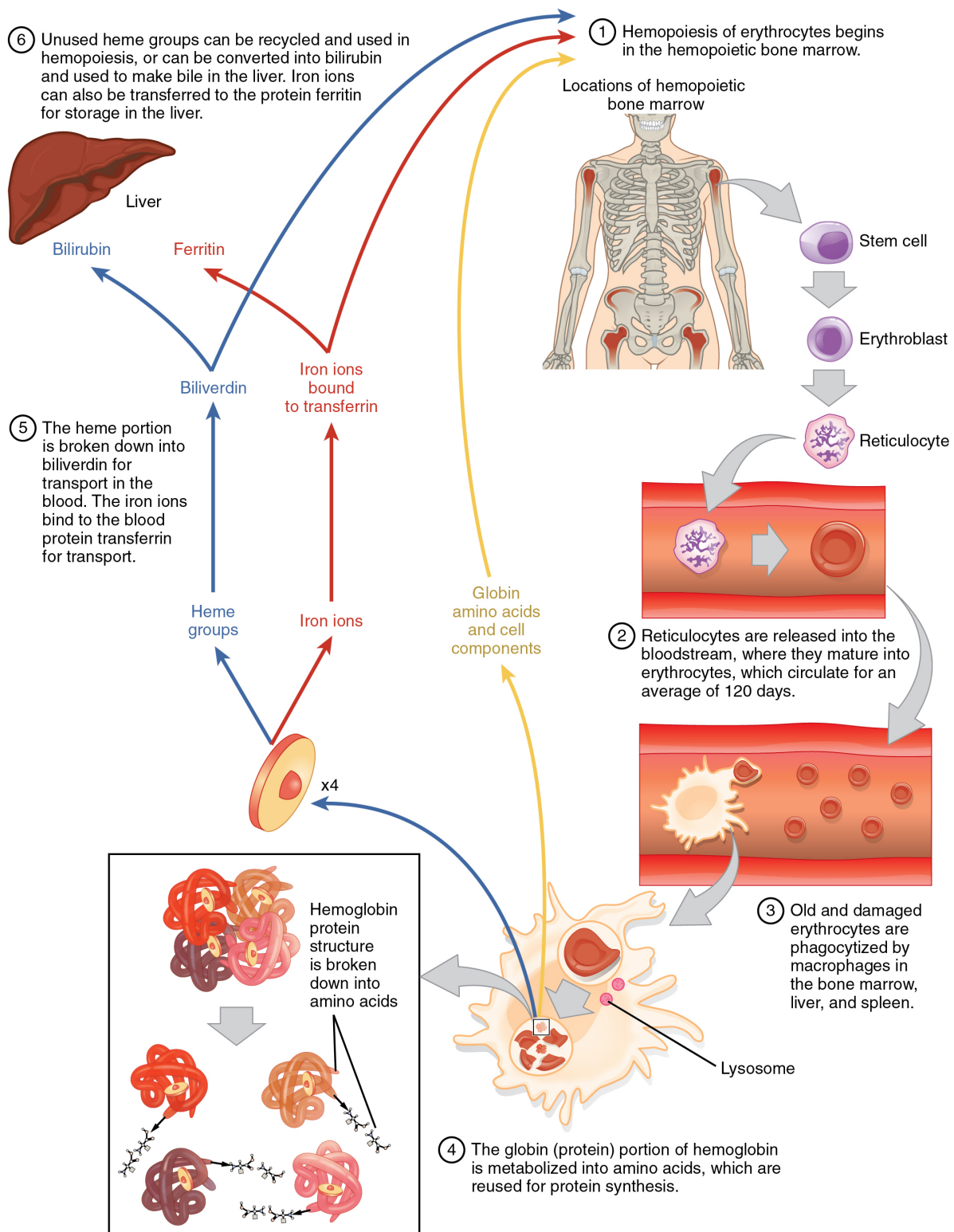
Erythrocytes live up to 120 days in the circulation, after which the worn-out cells are removed by a type of myeloid phagocytic cell called a **macrophage**, located primarily within the bone marrow, liver, and spleen. The components of the degraded erythrocytes' hemoglobin are further processed as follows:

- Globin, the protein portion of hemoglobin, is broken down into amino acids, which can be sent back to the bone marrow to be used in the production of new erythrocytes. Hemoglobin that is not phagocytized is broken down in the circulation, releasing alpha and beta chains that are removed from circulation by the kidneys.
- The iron contained in the heme portion of hemoglobin may be stored in the liver or spleen, primarily in the form of ferritin or hemosiderin, or carried through the bloodstream by transferrin to the red bone marrow for recycling into new erythrocytes.
- The non-iron portion of heme is degraded into the waste product **biliverdin**, a green pigment, and then into another waste product,

bilirubin, a yellow pigment. Bilirubin binds to albumin and travels in the blood to the liver, which uses it in the manufacture of bile, a compound released into the intestines to help emulsify dietary fats. In the large intestine, bacteria breaks the bilirubin apart from the bile and converts it to urobilinogen and then into stercobilin. It is then eliminated from the body in the feces. Broad-spectrum antibiotics typically eliminate these bacteria as well and may alter the color of feces. The kidneys also remove any circulating bilirubin and other related metabolic byproducts such as urobilins and secrete them into the urine.

The breakdown pigments formed from the destruction of hemoglobin can be seen in a variety of situations. At the site of an injury, biliverdin from damaged RBCs produces some of the dramatic colors associated with bruising. With a failing liver, bilirubin cannot be removed effectively from circulation and causes the body to assume a yellowish tinge associated with jaundice. Stercobilins within the feces produce the typical brown color associated with this waste. And the yellow of urine is associated with the urobilins.

The erythrocyte lifecycle is summarized in [\[link\]](#).
Erythrocyte Lifecycle



Erythrocytes are produced in the bone marrow and sent into the circulation. At the end of their lifecycle, they are destroyed by

macrophages, and their components are recycled.

Disorders of Erythrocytes

The size, shape, and number of erythrocytes, and the number of hemoglobin molecules can have a major impact on a person's health. When the number of RBCs or hemoglobin is deficient, the general condition is called **anemia**. There are more than 400 types of anemia and more than 3.5 million Americans suffer from this condition. Anemia can be broken down into three major groups: those caused by blood loss, those caused by faulty or decreased RBC production, and those caused by excessive destruction of RBCs. Clinicians often use two groupings in diagnosis: The kinetic approach focuses on evaluating the production, destruction, and removal of RBCs, whereas the morphological approach examines the RBCs themselves, paying particular emphasis to their size. A common test is the mean corpuscle volume (MCV), which measures size. Normal-sized cells are referred to as normocytic, smaller-than-normal cells are referred to as microcytic, and larger-than-normal cells are referred to as macrocytic. Reticulocyte counts are also important and may reveal inadequate production of RBCs. The effects of the various anemias are widespread, because reduced numbers of RBCs or hemoglobin will result in lower levels of oxygen being delivered to body tissues. Since oxygen is required for tissue functioning, anemia produces fatigue, lethargy, and an increased risk for infection. An oxygen deficit in the brain impairs the ability to think clearly, and may prompt headaches and irritability. Lack of oxygen leaves the patient short of breath, even as the heart and lungs work harder in response to the deficit.

Blood loss anemias are fairly straightforward. In addition to bleeding from wounds or other lesions, these forms of anemia may be due to ulcers, hemorrhoids, inflammation of the stomach (gastritis), and some cancers of the gastrointestinal tract. The excessive use of aspirin or other nonsteroidal anti-inflammatory drugs such as ibuprofen can trigger ulceration and gastritis. Excessive menstruation and loss of blood during childbirth are also potential causes.

Anemias caused by faulty or decreased RBC production include sickle cell anemia, iron deficiency anemia, vitamin deficiency anemia, and diseases of the bone marrow and stem cells.

- A characteristic change in the shape of erythrocytes is seen in **sickle cell disease** (also referred to as sickle cell anemia). A genetic disorder, it is caused by production of an abnormal type of hemoglobin, called hemoglobin S, which delivers less oxygen to tissues and causes erythrocytes to assume a sickle (or crescent) shape, especially at low oxygen concentrations ([\[link\]](#)). These abnormally shaped cells can then become lodged in narrow capillaries because they are unable to fold in on themselves to squeeze through, blocking blood flow to tissues and causing a variety of serious problems from painful joints to delayed growth and even blindness and cerebrovascular accidents (strokes). Sickle cell anemia is a genetic condition particularly found in individuals of African descent.

Sickle Cells



Sickle cell anemia is caused by a mutation in one of the hemoglobin genes. Erythrocytes produce an abnormal type of

hemoglobin, which causes the cell to take on a sickle or crescent shape. (credit: Janice Haney Carr)

- Iron deficiency anemia is the most common type and results when the amount of available iron is insufficient to allow production of sufficient heme. This condition can occur in individuals with a deficiency of iron in the diet and is especially common in teens and children as well as in vegans and vegetarians. Additionally, iron deficiency anemia may be caused by either an inability to absorb and transport iron or slow, chronic bleeding.
- Vitamin-deficient anemias generally involve insufficient vitamin B12 and folate.
 - Megaloblastic anemia involves a deficiency of vitamin B12 and/or folate, and often involves diets deficient in these essential nutrients. Lack of meat or a viable alternate source, and overcooking or eating insufficient amounts of vegetables may lead to a lack of folate.
 - Pernicious anemia is caused by poor absorption of vitamin B12 and is often seen in patients with Crohn's disease (a severe intestinal disorder often treated by surgery), surgical removal of the intestines or stomach (common in some weight loss surgeries), intestinal parasites, and AIDS.
 - Pregnancies, some medications, excessive alcohol consumption, and some diseases such as celiac disease are also associated with vitamin deficiencies. It is essential to provide sufficient folic acid during the early stages of pregnancy to reduce the risk of neurological defects, including spina bifida, a failure of the neural tube to close.
- Assorted disease processes can also interfere with the production and formation of RBCs and hemoglobin. If myeloid stem cells are

defective or replaced by cancer cells, there will be insufficient quantities of RBCs produced.

- Aplastic anemia is the condition in which there are deficient numbers of RBC stem cells. Aplastic anemia is often inherited, or it may be triggered by radiation, medication, chemotherapy, or infection.
- **Thalassemia** is an inherited condition typically occurring in individuals from the Middle East, the Mediterranean, African, and Southeast Asia, in which maturation of the RBCs does not proceed normally. The most severe form is called Cooley's anemia.
- Lead exposure from industrial sources or even dust from paint chips of iron-containing paints or pottery that has not been properly glazed may also lead to destruction of the red marrow.
- Various disease processes also can lead to anemias. These include chronic kidney diseases often associated with a decreased production of EPO, hypothyroidism, some forms of cancer, lupus, and rheumatoid arthritis.

In contrast to anemia, an elevated RBC count is called **polycythemia** and is detected in a patient's elevated hematocrit. It can occur transiently in a person who is dehydrated; when water intake is inadequate or water losses are excessive, the plasma volume falls. As a result, the hematocrit rises. For reasons mentioned earlier, a mild form of polycythemia is chronic but normal in people living at high altitudes. Some elite athletes train at high elevations specifically to induce this phenomenon. Finally, a type of bone marrow disease called polycythemia vera (from the Greek vera = "true") causes an excessive production of immature erythrocytes. Polycythemia vera can dangerously elevate the viscosity of blood, raising blood pressure and making it more difficult for the heart to pump blood throughout the body. It is a relatively rare disease that occurs more often in men than women, and is more likely to be present in elderly patients those over 60 years of age.

Chapter Review

The most abundant formed elements in blood, erythrocytes are red, biconcave disks packed with an oxygen-carrying compound called hemoglobin. The hemoglobin molecule contains four globin proteins bound to a pigment molecule called heme, which contains an ion of iron. In the bloodstream, iron picks up oxygen in the lungs and drops it off in the tissues; the amino acids in hemoglobin then transport carbon dioxide from the tissues back to the lungs. Erythrocytes live only 120 days on average, and thus must be continually replaced. Worn-out erythrocytes are phagocytized by macrophages and their hemoglobin is broken down. The breakdown products are recycled or removed as wastes: Globin is broken down into amino acids for synthesis of new proteins; iron is stored in the liver or spleen or used by the bone marrow for production of new erythrocytes; and the remnants of heme are converted into bilirubin, or other waste products that are taken up by the liver and excreted in the bile or removed by the kidneys. Anemia is a deficiency of RBCs or hemoglobin, whereas polycythemia is an excess of RBCs.

Review Questions

Exercise:

Problem:

Which of the following statements about mature, circulating erythrocytes is true?

- a. They have no nucleus.
- b. They are packed with mitochondria.
- c. They survive for an average of 4 days.
- d. All of the above

Solution:

A

Exercise:

Problem: A molecule of hemoglobin _____.

- a. is shaped like a biconcave disk packed almost entirely with iron
- b. contains four glycoprotein units studded with oxygen
- c. consists of four globin proteins, each bound to a molecule of heme
- d. can carry up to 120 molecules of oxygen

Solution:

C

Exercise:

Problem:

The production of healthy erythrocytes depends upon the availability of _____.

- a. copper
- b. zinc
- c. vitamin B₁₂
- d. copper, zinc, and vitamin B₁₂

Solution:

D

Exercise:

Problem:

Aging and damaged erythrocytes are removed from the circulation by _____.

- a. myeloblasts
- b. monocytes

- c. macrophages
 - d. mast cells
-

Solution:

C

Exercise:

Problem:

A patient has been suffering for 2 months with a chronic, watery diarrhea. A blood test is likely to reveal _____.

- a. a hematocrit below 30 percent
 - b. hypoxemia
 - c. anemia
 - d. polycythemia
-

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

A young woman has been experiencing unusually heavy menstrual bleeding for several years. She follows a strict vegan diet (no animal foods). She is at risk for what disorder, and why?

Solution:

She is at risk for anemia, because her unusually heavy menstrual bleeding results in excessive loss of erythrocytes each month. At the

same time, her vegan diet means that she does not have dietary sources of heme iron. The non-heme iron she consumes in plant foods is not as well absorbed as heme iron.

Exercise:**Problem:**

A patient has thalassemia, a genetic disorder characterized by abnormal synthesis of globin proteins and excessive destruction of erythrocytes. This patient is jaundiced and is found to have an excessive level of bilirubin in his blood. Explain the connection.

Solution:

Bilirubin is a breakdown product of the non-iron component of heme, which is cleaved from globin when erythrocytes are degraded. Excessive erythrocyte destruction would deposit excessive bilirubin in the blood. Bilirubin is a yellowish pigment, and high blood levels can manifest as yellowed skin.

Glossary

anemia

deficiency of red blood cells or hemoglobin

bilirubin

yellowish bile pigment produced when iron is removed from heme and is further broken down into waste products

biliverdin

green bile pigment produced when the non-iron portion of heme is degraded into a waste product; converted to bilirubin in the liver

carbaminohemoglobin

compound of carbon dioxide and hemoglobin, and one of the ways in which carbon dioxide is carried in the blood

deoxyhemoglobin

molecule of hemoglobin without an oxygen molecule bound to it

erythrocyte

(also, red blood cell) mature myeloid blood cell that is composed mostly of hemoglobin and functions primarily in the transportation of oxygen and carbon dioxide

ferritin

protein-containing storage form of iron found in the bone marrow, liver, and spleen

globin

heme-containing globular protein that is a constituent of hemoglobin

heme

red, iron-containing pigment to which oxygen binds in hemoglobin

hemoglobin

oxygen-carrying compound in erythrocytes

hemosiderin

protein-containing storage form of iron found in the bone marrow, liver, and spleen

hypoxemia

below-normal level of oxygen saturation of blood (typically <95 percent)

macrophage

phagocytic cell of the myeloid lineage; a matured monocyte

oxyhemoglobin

molecule of hemoglobin to which oxygen is bound

polycythemia

elevated level of hemoglobin, whether adaptive or pathological

reticulocyte

immature erythrocyte that may still contain fragments of organelles

sickle cell disease

(also, sickle cell anemia) inherited blood disorder in which hemoglobin molecules are malformed, leading to the breakdown of RBCs that take on a characteristic sickle shape

thalassemia

inherited blood disorder in which maturation of RBCs does not proceed normally, leading to abnormal formation of hemoglobin and the destruction of RBCs

transferrin

plasma protein that binds reversibly to iron and distributes it throughout the body

Leukocytes and Platelets

By the end of this section, you will be able to:

- Describe the general characteristics of leukocytes
- Classify leukocytes according to their lineage, their main structural features, and their primary functions
- Discuss the most common malignancies involving leukocytes
- Identify the lineage, basic structure, and function of platelets

The **leukocyte**, commonly known as a white blood cell (or WBC), is a major component of the body's defenses against disease. Leukocytes protect the body against invading microorganisms and body cells with mutated DNA, and they clean up debris. Platelets are essential for the repair of blood vessels when damage to them has occurred; they also provide growth factors for healing and repair. See [\[link\]](#) for a summary of leukocytes and platelets.

Characteristics of Leukocytes

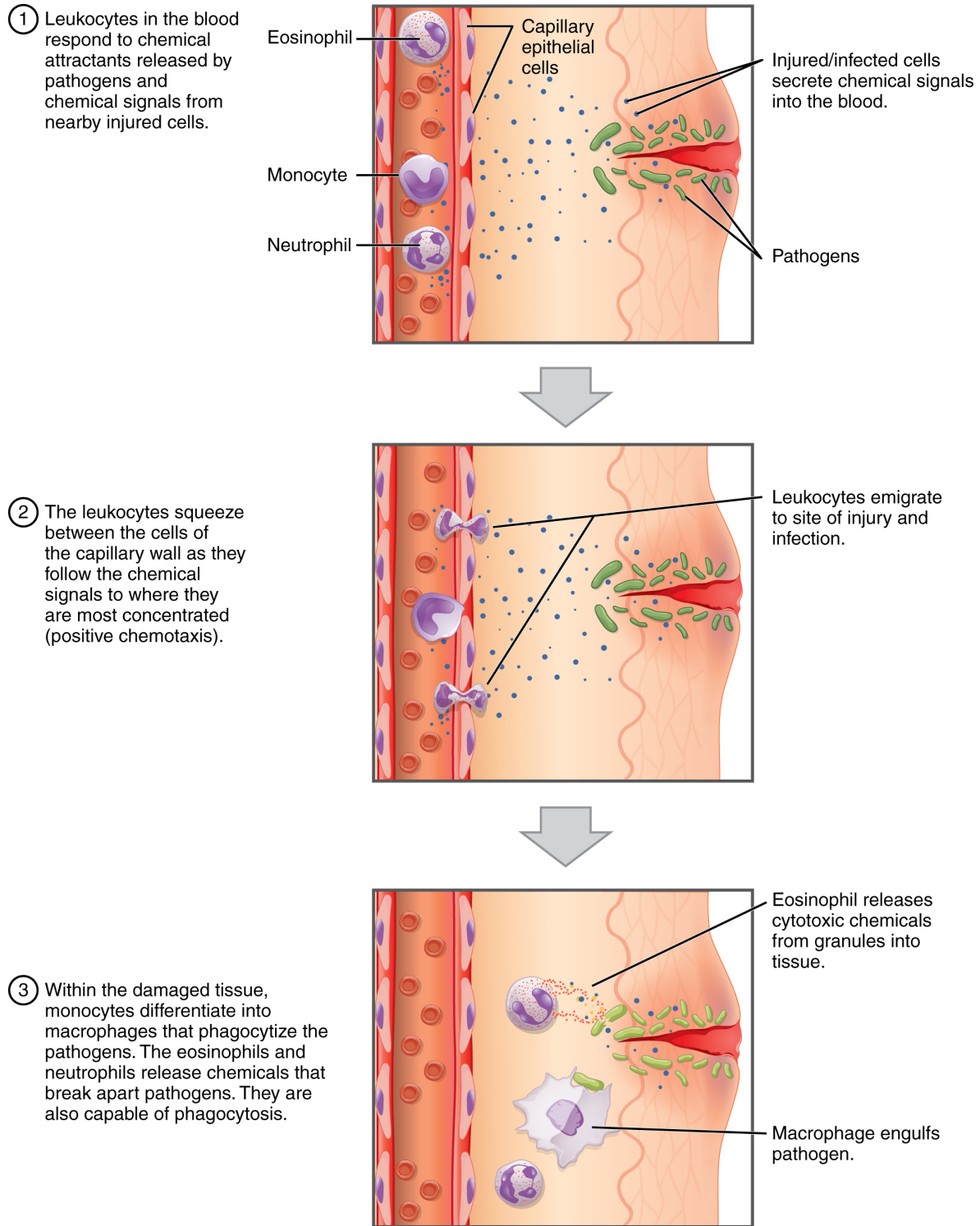
Although leukocytes and erythrocytes both originate from hematopoietic stem cells in the bone marrow, they are very different from each other in many significant ways. For instance, leukocytes are far less numerous than erythrocytes: Typically there are only 5000 to 10,000 per μL . They are also larger than erythrocytes and are the only formed elements that are complete cells, possessing a nucleus and organelles. And although there is just one type of erythrocyte, there are many types of leukocytes. Most of these types have a much shorter lifespan than that of erythrocytes, some as short as a few hours or even a few minutes in the case of acute infection.

One of the most distinctive characteristics of leukocytes is their movement. Whereas erythrocytes spend their days circulating within the blood vessels, leukocytes routinely leave the bloodstream to perform their defensive functions in the body's tissues. For leukocytes, the vascular network is simply a highway they travel and soon exit to reach their true destination. When they arrive, they are often given distinct names, such as macrophage or microglia, depending on their function. As shown in [\[link\]](#), they leave the capillaries—the smallest blood vessels—or other small vessels through a

process known as **emigration** (from the Latin for “removal”) or **diapedesis** (dia- = “through”; -pedan = “to leap”) in which they squeeze through adjacent cells in a blood vessel wall.

Once they have exited the capillaries, some leukocytes will take up fixed positions in lymphatic tissue, bone marrow, the spleen, the thymus, or other organs. Others will move about through the tissue spaces very much like amoebas, continuously extending their plasma membranes, sometimes wandering freely, and sometimes moving toward the direction in which they are drawn by chemical signals. This attracting of leukocytes occurs because of **positive chemotaxis** (literally “movement in response to chemicals”), a phenomenon in which injured or infected cells and nearby leukocytes emit the equivalent of a chemical “911” call, attracting more leukocytes to the site. In clinical medicine, the differential counts of the types and percentages of leukocytes present are often key indicators in making a diagnosis and selecting a treatment.

Emigration



Leukocytes exit the blood vessel and then move through the connective tissue of the dermis toward the site of a wound. Some leukocytes, such as the eosinophil and neutrophil, are characterized

as granular leukocytes. They release chemicals from their granules that destroy pathogens; they are also capable of phagocytosis. The monocyte, an agranular leukocyte, differentiates into a macrophage that then phagocytizes the pathogens.

Classification of Leukocytes

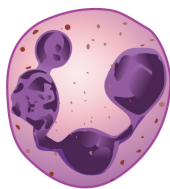
When scientists first began to observe stained blood slides, it quickly became evident that leukocytes could be divided into two groups, according to whether their cytoplasm contained highly visible granules:

- **Granular leukocytes** contain abundant granules within the cytoplasm. They include neutrophils, eosinophils, and basophils (you can view their lineage from myeloid stem cells in [\[link\]](#)).
- While granules are not totally lacking in **agranular leukocytes**, they are far fewer and less obvious. Agranular leukocytes include monocytes, which mature into macrophages that are phagocytic, and lymphocytes, which arise from the lymphoid stem cell line.

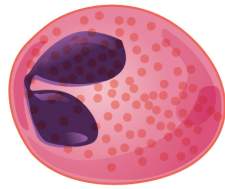
Granular Leukocytes

We will consider the granular leukocytes in order from most common to least common. All of these are produced in the red bone marrow and have a short lifespan of hours to days. They typically have a lobed nucleus and are classified according to which type of stain best highlights their granules ([\[link\]](#)).

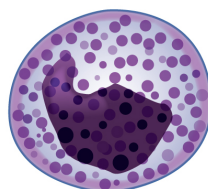
Granular Leukocytes



Neutrophil



Eosinophil



Basophil

A neutrophil has small granules that stain light lilac and a nucleus with two to five lobes. An eosinophil's granules are slightly larger and stain reddish-orange, and its nucleus has two to three lobes. A basophil has large granules that stain dark blue to purple and a two-lobed nucleus.

The most common of all the leukocytes, **neutrophils** will normally comprise 50–70 percent of total leukocyte count. They are 10–12 μm in diameter, significantly larger than erythrocytes. They are called neutrophils because their granules show up most clearly with stains that are chemically neutral (neither acidic nor basic). The granules are numerous but quite fine and normally appear light lilac. The nucleus has a distinct lobed appearance and may have two to five lobes, the number increasing with the age of the cell. Older neutrophils have increasing numbers of lobes and are often referred to as **polymorphonuclear** (a nucleus with many forms), or simply “polys.” Younger and immature neutrophils begin to develop lobes and are known as “bands.”

Neutrophils are rapid responders to the site of infection and are efficient phagocytes with a preference for bacteria. Their granules include **lysozyme**, an enzyme capable of lysing, or breaking down, bacterial cell walls; oxidants such as hydrogen peroxide; and **defensins**, proteins that bind to and puncture bacterial and fungal plasma membranes, so that the cell contents leak out. Abnormally high counts of neutrophils indicate infection and/or inflammation, particularly triggered by bacteria, but are also found in burn patients and others experiencing unusual stress. A burn injury increases the proliferation of neutrophils in order to fight off infection that can result from the destruction of the barrier of the skin. Low counts may be caused by drug toxicity and other disorders, and may increase an individual's susceptibility to infection.

Eosinophils typically represent 2–4 percent of total leukocyte count. They are also 10–12 μm in diameter. The granules of eosinophils stain best with

an acidic stain known as eosin. The nucleus of the eosinophil will typically have two to three lobes and, if stained properly, the granules will have a distinct red to orange color.

The granules of eosinophils include antihistamine molecules, which counteract the activities of histamines, inflammatory chemicals produced by basophils and mast cells. Some eosinophil granules contain molecules toxic to parasitic worms, which can enter the body through the integument, or when an individual consumes raw or undercooked fish or meat. Eosinophils are also capable of phagocytosis and are particularly effective when antibodies bind to the target and form an antigen-antibody complex. High counts of eosinophils are typical of patients experiencing allergies, parasitic worm infestations, and some autoimmune diseases. Low counts may be due to drug toxicity and stress.

Basophils are the least common leukocytes, typically comprising less than one percent of the total leukocyte count. They are slightly smaller than neutrophils and eosinophils at 8–10 μm in diameter. The granules of basophils stain best with basic (alkaline) stains. Basophils contain large granules that pick up a dark blue stain and are so common they may make it difficult to see the two-lobed nucleus.

In general, basophils intensify the inflammatory response. They share this trait with mast cells. In the past, mast cells were considered to be basophils that left the circulation. However, this appears not to be the case, as the two cell types develop from different lineages.

The granules of basophils release histamines, which contribute to inflammation, and heparin, which opposes blood clotting. High counts of basophils are associated with allergies, parasitic infections, and hypothyroidism. Low counts are associated with pregnancy, stress, and hyperthyroidism.

Agranular Leukocytes

Agranular leukocytes contain smaller, less-visible granules in their cytoplasm than do granular leukocytes. The nucleus is simple in shape, sometimes with an indentation but without distinct lobes. There are two major types of agranulocytes: lymphocytes and monocytes (see [\[link\]](#)).

Lymphocytes are the only formed element of blood that arises from lymphoid stem cells. Although they form initially in the bone marrow, much of their subsequent development and reproduction occurs in the lymphatic tissues. Lymphocytes are the second most common type of leukocyte, accounting for about 20–30 percent of all leukocytes, and are essential for the immune response. The size range of lymphocytes is quite extensive, with some authorities recognizing two size classes and others three. Typically, the large cells are 10–14 μm and have a smaller nucleus-to-cytoplasm ratio and more granules. The smaller cells are typically 6–9 μm with a larger volume of nucleus to cytoplasm, creating a “halo” effect. A few cells may fall outside these ranges, at 14–17 μm . This finding has led to the three size range classification.

The three major groups of lymphocytes include natural killer cells, B cells, and T cells. **Natural killer (NK) cells** are capable of recognizing cells that do not express “self” proteins on their plasma membrane or that contain foreign or abnormal markers. These “nonself” cells include cancer cells, cells infected with a virus, and other cells with atypical surface proteins. Thus, they provide generalized, nonspecific immunity. The larger lymphocytes are typically NK cells.

B cells and T cells, also called **B lymphocytes** and **T lymphocytes**, play prominent roles in defending the body against specific pathogens (disease-causing microorganisms) and are involved in specific immunity. One form of B cells (plasma cells) produces the antibodies or immunoglobulins that bind to specific foreign or abnormal components of plasma membranes. This is also referred to as humoral (body fluid) immunity. T cells provide cellular-level immunity by physically attacking foreign or diseased cells. A **memory cell** is a variety of both B and T cells that forms after exposure to a pathogen and mounts rapid responses upon subsequent exposures. Unlike other leukocytes, memory cells live for many years. B cells undergo a maturation process in the bone marrow, whereas T cells undergo maturation

in the thymus. This site of the maturation process gives rise to the name B and T cells. The functions of lymphocytes are complex and will be covered in detail in the chapter covering the lymphatic system and immunity. Smaller lymphocytes are either B or T cells, although they cannot be differentiated in a normal blood smear.

Abnormally high lymphocyte counts are characteristic of viral infections as well as some types of cancer. Abnormally low lymphocyte counts are characteristic of prolonged (chronic) illness or immunosuppression, including that caused by HIV infection and drug therapies that often involve steroids.

Monocytes originate from myeloid stem cells. They normally represent 2–8 percent of the total leukocyte count. They are typically easily recognized by their large size of 12–20 μm and indented or horseshoe-shaped nuclei. Macrophages are monocytes that have left the circulation and phagocytize debris, foreign pathogens, worn-out erythrocytes, and many other dead, worn out, or damaged cells. Macrophages also release antimicrobial defensins and chemotactic chemicals that attract other leukocytes to the site of an infection. Some macrophages occupy fixed locations, whereas others wander through the tissue fluid.

Abnormally high counts of monocytes are associated with viral or fungal infections, tuberculosis, and some forms of leukemia and other chronic diseases. Abnormally low counts are typically caused by suppression of the bone marrow.

Lifecycle of Leukocytes

Most leukocytes have a relatively short lifespan, typically measured in hours or days. Production of all leukocytes begins in the bone marrow under the influence of CSFs and interleukins. Secondary production and maturation of lymphocytes occurs in specific regions of lymphatic tissue known as germinal centers. Lymphocytes are fully capable of mitosis and may produce clones of cells with identical properties. This capacity enables an individual to maintain immunity throughout life to many threats that have been encountered in the past.

Disorders of Leukocytes

Leukopenia is a condition in which too few leukocytes are produced. If this condition is pronounced, the individual may be unable to ward off disease. Excessive leukocyte proliferation is known as **leukocytosis**. Although leukocyte counts are high, the cells themselves are often nonfunctional, leaving the individual at increased risk for disease.

Leukemia is a cancer involving an abundance of leukocytes. It may involve only one specific type of leukocyte from either the myeloid line (myelocytic leukemia) or the lymphoid line (lymphocytic leukemia). In chronic leukemia, mature leukocytes accumulate and fail to die. In acute leukemia, there is an overproduction of young, immature leukocytes. In both conditions the cells do not function properly.

Lymphoma is a form of cancer in which masses of malignant T and/or B lymphocytes collect in lymph nodes, the spleen, the liver, and other tissues. As in leukemia, the malignant leukocytes do not function properly, and the patient is vulnerable to infection. Some forms of lymphoma tend to progress slowly and respond well to treatment. Others tend to progress quickly and require aggressive treatment, without which they are rapidly fatal.

Platelets

You may occasionally see platelets referred to as **thrombocytes**, but because this name suggests they are a type of cell, it is not accurate. A platelet is not a cell but rather a fragment of the cytoplasm of a cell called a **megakaryocyte** that is surrounded by a plasma membrane. Megakaryocytes are descended from myeloid stem cells (see [\[link\]](#)) and are large, typically 50–100 μm in diameter, and contain an enlarged, lobed nucleus. As noted earlier, thrombopoietin, a glycoprotein secreted by the kidneys and liver, stimulates the proliferation of megakaryoblasts, which mature into megakaryocytes. These remain within bone marrow tissue ([\[link\]](#)) and ultimately form platelet-precursor extensions that extend through the walls of bone marrow capillaries to release into the circulation thousands of cytoplasmic fragments, each enclosed by a bit of plasma membrane. These

enclosed fragments are platelets. Each megakaryocyte releases 2000–3000 platelets during its lifespan. Following platelet release, megakaryocyte remnants, which are little more than a cell nucleus, are consumed by macrophages.

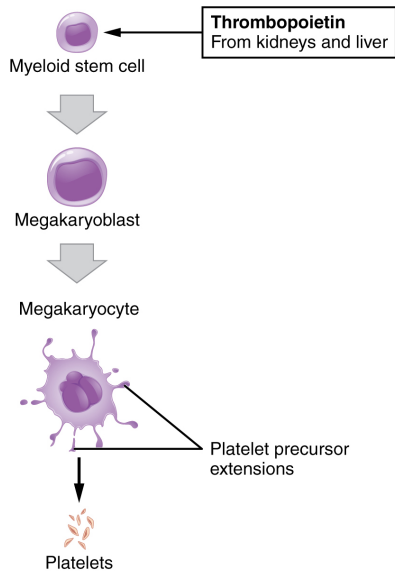
Platelets are relatively small, 2–4 μm in diameter, but numerous, with typically 150,000–160,000 per μL of blood. After entering the circulation, approximately one-third migrate to the spleen for storage for later release in response to any rupture in a blood vessel. They then become activated to perform their primary function, which is to limit blood loss. Platelets remain only about 10 days, then are phagocytized by macrophages.

Platelets are critical to hemostasis, the stoppage of blood flow following damage to a vessel. They also secrete a variety of growth factors essential for growth and repair of tissue, particularly connective tissue. Infusions of concentrated platelets are now being used in some therapies to stimulate healing.

Disorders of Platelets

Thrombocytosis is a condition in which there are too many platelets. This may trigger formation of unwanted blood clots (thrombosis), a potentially fatal disorder. If there is an insufficient number of platelets, called **thrombocytopenia**, blood may not clot properly, and excessive bleeding may result.

Platelets



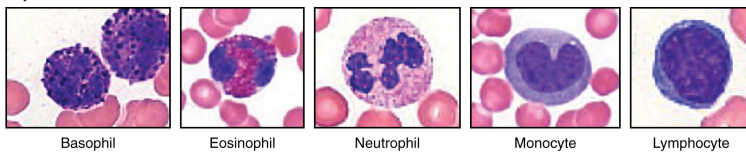
Platelets are derived from cells called megakaryocytes.

Note:



Leukocytes

Key



(Micrographs provided by the Regents of

University of Michigan Medical School ©
2012)

View University of Michigan Webscopes at
[http://virtualslides.med.umich.edu/Histology/Cardiovascular%20System/081-2_HISTO_40X.svs/view.apml?](http://virtualslides.med.umich.edu/Histology/Cardiovascular%20System/081-2_HISTO_40X.svs/view.apml?cwidth=860&cheight=733&chost=virtualslides.med.umich.edu&listview=1&title=&csis=1)

[cwidth=860&cheight=733&chost=virtualslides.med.umich.edu&listview=1&title=&csis=1](http://virtualslides.med.umich.edu/Histology/Cardiovascular%20System/081-2_HISTO_40X.svs/view.apml?cwidth=860&cheight=733&chost=virtualslides.med.umich.edu&listview=1&title=&csis=1) and explore the blood slides in greater detail. The Webscope feature allows you to move the slides as you would with a mechanical stage. You can increase and decrease the magnification. There is a chance to review each of the leukocytes individually after you have attempted to identify them from the first two blood smears. In addition, there are a few multiple choice questions.

Are you able to recognize and identify the various formed elements? You will need to do this in a systematic manner, scanning along the image. The standard method is to use a grid, but this is not possible with this resource. Try constructing a simple table with each leukocyte type and then making a mark for each cell type you identify. Attempt to classify at least 50 and perhaps as many as 100 different cells. Based on the percentage of cells that you count, do the numbers represent a normal blood smear or does something appear to be abnormal?

Chapter Review

Leukocytes function in body defenses. They squeeze out of the walls of blood vessels through emigration or diapedesis, then may move through tissue fluid or become attached to various organs where they fight against pathogenic organisms, diseased cells, or other threats to health. Granular leukocytes, which include neutrophils, eosinophils, and basophils, originate with myeloid stem cells, as do the agranular monocytes. The other agranular leukocytes, NK cells, B cells, and T cells, arise from the lymphoid stem cell line. The most abundant leukocytes are the neutrophils, which are first responders to infections, especially with bacteria. About 20–30 percent of all leukocytes are lymphocytes, which are critical to the

body's defense against specific threats. Leukemia and lymphoma are malignancies involving leukocytes. Platelets are fragments of cells known as megakaryocytes that dwell within the bone marrow. While many platelets are stored in the spleen, others enter the circulation and are essential for hemostasis; they also produce several growth factors important for repair and healing.

Interactive Link Questions

Exercise:

Problem:

[\[link\]](#) Are you able to recognize and identify the various formed elements? You will need to do this in a systematic manner, scanning along the image. The standard method is to use a grid, but this is not possible with this resource. Try constructing a simple table with each leukocyte type and then making a mark for each cell type you identify. Attempt to classify at least 50 and perhaps as many as 100 different cells. Based on the percentage of cells that you count, do the numbers represent a normal blood smear or does something appear to be abnormal?

Solution:

[\[link\]](#) This should appear to be a normal blood smear.

Review Questions

Exercise:

Problem:

The process by which leukocytes squeeze through adjacent cells in a blood vessel wall is called _____.

- a. leukocytosis
- b. positive chemotaxis

- c. emigration
 - d. cytoplasmic extending
-

Solution:

C

Exercise:

Problem: Which of the following describes a neutrophil?

- a. abundant, agranular, especially effective against cancer cells
 - b. abundant, granular, especially effective against bacteria
 - c. rare, agranular, releases antimicrobial defensins
 - d. rare, granular, contains multiple granules packed with histamine
-

Solution:

B

Exercise:

Problem: T and B lymphocytes _____.

- a. are polymorphonuclear
 - b. are involved with specific immune function
 - c. proliferate excessively in leukopenia
 - d. are most active against parasitic worms
-

Solution:

B

Exercise:

Problem:

A patient has been experiencing severe, persistent allergy symptoms that are reduced when she takes an antihistamine. Before the treatment, this patient was likely to have had increased activity of which leukocyte?

- a. basophils
- b. neutrophils
- c. monocytes
- d. natural killer cells

Solution:

A

Exercise:

Problem:Thrombocytes are more accurately called _____.

- a. clotting factors
- b. megakaryoblasts
- c. megakaryocytes
- d. platelets

Solution:

D

Critical Thinking Questions**Exercise:**

Problem:

One of the more common adverse effects of cancer chemotherapy is the destruction of leukocytes. Before his next scheduled chemotherapy treatment, a patient undergoes a blood test called an absolute neutrophil count (ANC), which reveals that his neutrophil count is 1900 cells per microliter. Would his healthcare team be likely to proceed with his chemotherapy treatment? Why?

Solution:

A neutrophil count below 1800 cells per microliter is considered abnormal. Thus, this patient's ANC is at the low end of the normal range and there would be no reason to delay chemotherapy. In clinical practice, most patients are given chemotherapy if their ANC is above 1000.

Exercise:**Problem:**

A patient was admitted to the burn unit the previous evening suffering from a severe burn involving his left upper extremity and shoulder. A blood test reveals that he is experiencing leukocytosis. Why is this an expected finding?

Solution:

Any severe stress can increase the leukocyte count, resulting in leukocytosis. A burn is especially likely to increase the proliferation of leukocytes in order to ward off infection, a significant risk when the barrier function of the skin is destroyed.

Glossary

agranular leukocytes

leukocytes with few granules in their cytoplasm; specifically, monocytes, lymphocytes, and NK cells

B lymphocytes

(also, B cells) lymphocytes that defend the body against specific pathogens and thereby provide specific immunity

basophils

granulocytes that stain with a basic (alkaline) stain and store histamine and heparin

defensins

antimicrobial proteins released from neutrophils and macrophages that create openings in the plasma membranes to kill cells

diapedesis

(also, emigration) process by which leukocytes squeeze through adjacent cells in a blood vessel wall to enter tissues

emigration

(also, diapedesis) process by which leukocytes squeeze through adjacent cells in a blood vessel wall to enter tissues

eosinophils

granulocytes that stain with eosin; they release antihistamines and are especially active against parasitic worms

granular leukocytes

leukocytes with abundant granules in their cytoplasm; specifically, neutrophils, eosinophils, and basophils

leukemia

cancer involving leukocytes

leukocyte

(also, white blood cell) colorless, nucleated blood cell, the chief function of which is to protect the body from disease

leukocytosis

excessive leukocyte proliferation

leukopenia

below-normal production of leukocytes

lymphocytes

agranular leukocytes of the lymphoid stem cell line, many of which function in specific immunity

lymphoma

form of cancer in which masses of malignant T and/or B lymphocytes collect in lymph nodes, the spleen, the liver, and other tissues

lysozyme

digestive enzyme with bactericidal properties

megakaryocyte

bone marrow cell that produces platelets

memory cell

type of B or T lymphocyte that forms after exposure to a pathogen

monocytes

agranular leukocytes of the myeloid stem cell line that circulate in the bloodstream; tissue monocytes are macrophages

natural killer (NK) cells

cytotoxic lymphocytes capable of recognizing cells that do not express “self” proteins on their plasma membrane or that contain foreign or abnormal markers; provide generalized, nonspecific immunity

neutrophils

granulocytes that stain with a neutral dye and are the most numerous of the leukocytes; especially active against bacteria

polymorphonuclear

having a lobed nucleus, as seen in some leukocytes

positive chemotaxis

process in which a cell is attracted to move in the direction of chemical stimuli

T lymphocytes

(also, T cells) lymphocytes that provide cellular-level immunity by physically attacking foreign or diseased cells

thrombocytes

platelets, one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

thrombocytopenia

condition in which there are too few platelets, resulting in abnormal bleeding (hemophilia)

thrombocytosis

condition in which there are too many platelets, resulting in abnormal clotting (thrombosis)

Hemostasis

By the end of this section, you will be able to:

- Describe the three mechanisms involved in hemostasis
- Explain how the extrinsic and intrinsic coagulation pathways lead to the common pathway, and the coagulation factors involved in each
- Discuss disorders affecting hemostasis

Platelets are key players in **hemostasis**, the process by which the body seals a ruptured blood vessel and prevents further loss of blood. Although rupture of larger vessels usually requires medical intervention, hemostasis is quite effective in dealing with small, simple wounds. There are three steps to the process: vascular spasm, the formation of a platelet plug, and coagulation (blood clotting). Failure of any of these steps will result in **hemorrhage**—excessive bleeding.

Vascular Spasm

When a vessel is severed or punctured, or when the wall of a vessel is damaged, vascular spasm occurs. In **vascular spasm**, the smooth muscle in the walls of the vessel contracts dramatically. This smooth muscle has both circular layers; larger vessels also have longitudinal layers. The circular layers tend to constrict the flow of blood, whereas the longitudinal layers, when present, draw the vessel back into the surrounding tissue, often making it more difficult for a surgeon to locate, clamp, and tie off a severed vessel. The vascular spasm response is believed to be triggered by several chemicals called endothelins that are released by vessel-lining cells and by pain receptors in response to vessel injury. This phenomenon typically lasts for up to 30 minutes, although it can last for hours.

Formation of the Platelet Plug

In the second step, platelets, which normally float free in the plasma, encounter the area of vessel rupture with the exposed underlying connective tissue and collagenous fibers. The platelets begin to clump together, become spiked and sticky, and bind to the exposed collagen and endothelial lining. This process is assisted by a glycoprotein in the blood plasma called von Willebrand factor, which helps stabilize the growing **platelet plug**. As platelets collect, they simultaneously release chemicals from their granules into the plasma that further contribute to hemostasis. Among the substances released by the platelets are:

- adenosine diphosphate (ADP), which helps additional platelets to adhere to the injury site, reinforcing and expanding the platelet plug
- serotonin, which maintains vasoconstriction

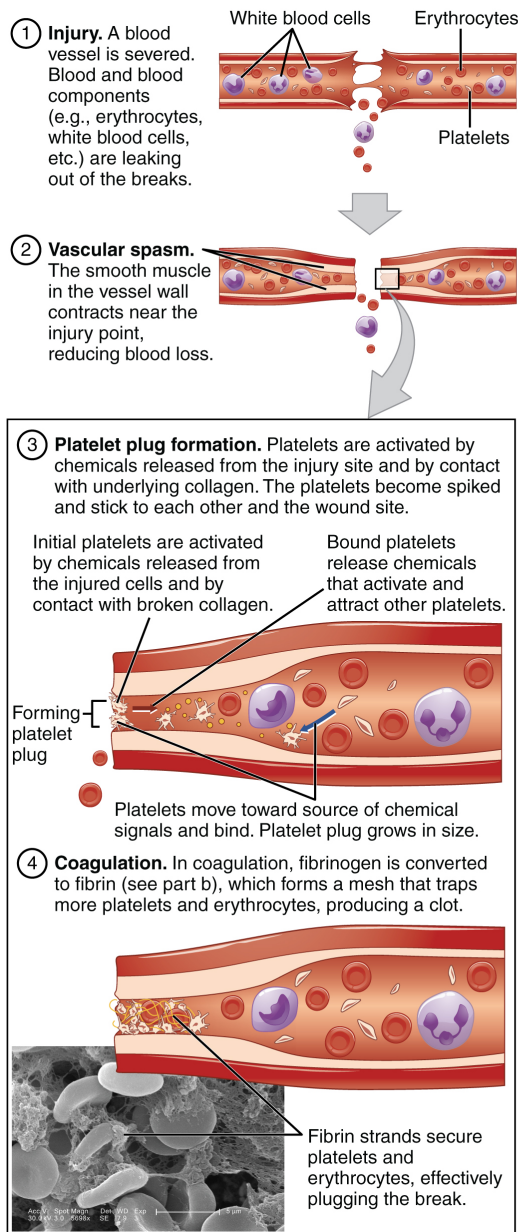
- prostaglandins and phospholipids, which also maintain vasoconstriction and help to activate further clotting chemicals, as discussed next

A platelet plug can temporarily seal a small opening in a blood vessel. Plug formation, in essence, buys the body time while more sophisticated and durable repairs are being made. In a similar manner, even modern naval warships still carry an assortment of wooden plugs to temporarily repair small breaches in their hulls until permanent repairs can be made.

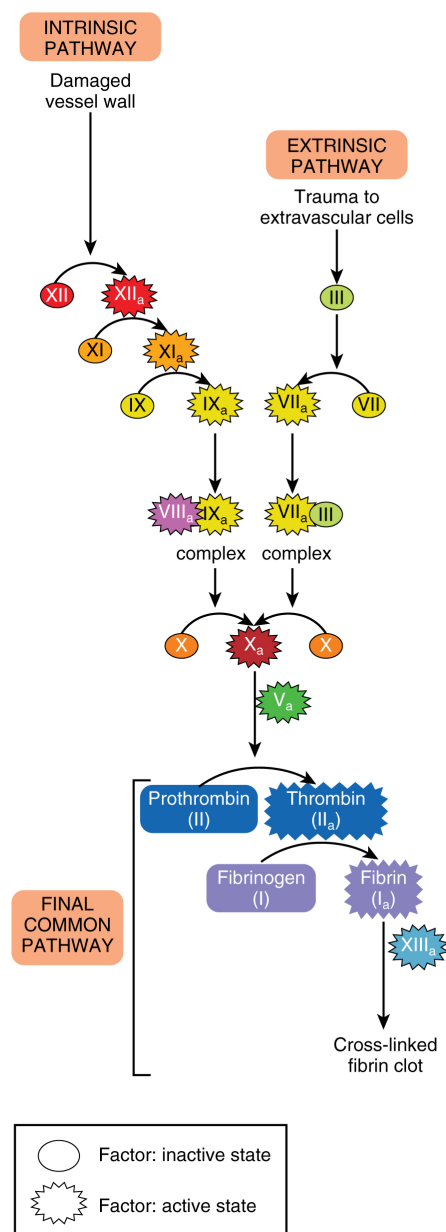
Coagulation

Those more sophisticated and more durable repairs are collectively called **coagulation**, the formation of a blood clot. The process is sometimes characterized as a cascade, because one event prompts the next as in a multi-level waterfall. The result is the production of a gelatinous but robust clot made up of a mesh of **fibrin**—an insoluble filamentous protein derived from fibrinogen, the plasma protein introduced earlier—in which platelets and blood cells are trapped. [\[link\]](#) summarizes the three steps of hemostasis.

Hemostasis



(a) The general steps of clotting



(b) Fibrin synthesis cascade

(a) An injury to a blood vessel initiates the process of hemostasis. Blood clotting involves three steps. First, vascular spasm constricts the flow of blood. Next, a platelet plug forms to temporarily seal small openings in the vessel. Coagulation then enables the repair of the vessel wall once the leakage of blood has stopped. (b) The synthesis of fibrin in blood clots involves either an intrinsic pathway or an extrinsic pathway, both of which lead to a common pathway.

(credit a: Kevin MacKenzie)

Clotting Factors Involved in Coagulation

In the coagulation cascade, chemicals called **clotting factors** (or coagulation factors) prompt reactions that activate still more coagulation factors. The process is complex, but is initiated along two basic pathways:

- The extrinsic pathway, which normally is triggered by trauma.
- The intrinsic pathway, which begins in the bloodstream and is triggered by internal damage to the wall of the vessel.

Both of these merge into a third pathway, referred to as the common pathway (see [\[link\]](#)**b**). All three pathways are dependent upon the 12 known clotting factors, including Ca^{2+} and vitamin K ([\[link\]](#)). Clotting factors are secreted primarily by the liver and the platelets. The liver requires the fat-soluble vitamin K to produce many of them. Vitamin K (along with biotin and folate) is somewhat unusual among vitamins in that it is not only consumed in the diet but is also synthesized by bacteria residing in the large intestine. The calcium ion, considered factor IV, is derived from the diet and from the breakdown of bone. Some recent evidence indicates that activation of various clotting factors occurs on specific receptor sites on the surfaces of platelets.

The 12 clotting factors are numbered I through XIII according to the order of their discovery. Factor VI was once believed to be a distinct clotting factor, but is now thought to be identical to factor V. Rather than renumber the other factors, factor VI was allowed to remain as a placeholder and also a reminder that knowledge changes over time.

| Clotting Factors | | | | |
|------------------|------------|------------------|--------|-------------------------------|
| Factor number | Name | Type of molecule | Source | Pathway(s) |
| I | Fibrinogen | Plasma protein | Liver | Common; converted into fibrin |

| Clotting Factors | | | | |
|-------------------------|--|--------------------------|---------------------------------|---|
| Factor number | Name | Type of molecule | Source | Pathway(s) |
| II | Prothrombin | Plasma protein | Liver* | Common; converted into thrombin |
| III | Tissue thromboplastin or tissue factor | Lipoprotein mixture | Damaged cells and platelets | Extrinsic |
| IV | Calcium ions | Inorganic ions in plasma | Diet, platelets, bone matrix | Entire process |
| V | Proaccelerin | Plasma protein | Liver, platelets | Extrinsic and intrinsic |
| VI | Not used | Not used | Not used | Not used |
| VII | Proconvertin | Plasma protein | Liver * | Extrinsic |
| VIII | Antihemolytic factor A | Plasma protein factor | Platelets and endothelial cells | Intrinsic; deficiency results in hemophilia A |
| IX | Antihemolytic factor B (plasma thromboplastin component) | Plasma protein | Liver* | Intrinsic; deficiency results in hemophilia B |

| Clotting Factors | | | | |
|------------------|---|------------------|------------------|---|
| Factor number | Name | Type of molecule | Source | Pathway(s) |
| X | Stuart–Prower factor (thrombokinas) | Protein | Liver* | Extrinsic and intrinsic |
| XI | Antihemolytic factor C (plasma thromboplastin antecedent) | Plasma protein | Liver | Intrinsic; deficiency results in hemophilia C |
| XII | Hageman factor | Plasma protein | Liver | Intrinsic; initiates clotting in vitro also activates plasmin |
| XIII | Fibrin-stabilizing factor | Plasma protein | Liver, platelets | Stabilizes fibrin; slows fibrinolysis |

*Vitamin K required.

Extrinsic Pathway

The quicker responding and more direct **extrinsic pathway** (also known as the **tissue factor** pathway) begins when damage occurs to the surrounding tissues, such as in a traumatic injury. Upon contact with blood plasma, the damaged extravascular cells, which are extrinsic to the bloodstream, release factor III (thromboplastin).

Sequentially, Ca^{2+} then factor VII (proconvertin), which is activated by factor III, are added, forming an enzyme complex. This enzyme complex leads to activation of factor X (Stuart–Prower factor), which activates the common pathway discussed below. The events in the extrinsic pathway are completed in a matter of seconds.

Intrinsic Pathway

The **intrinsic pathway** (also known as the contact activation pathway) is longer and more complex. In this case, the factors involved are intrinsic to (present within) the bloodstream. The pathway can be prompted by damage to the tissues, resulting from internal factors such as arterial disease; however, it is most often initiated when factor XII (Hageman factor) comes into contact with foreign materials, such as when a blood sample is put into a glass test tube. Within the body, factor XII is typically activated when it encounters negatively charged molecules, such as inorganic polymers and phosphate produced earlier in the series of intrinsic pathway reactions. Factor XII sets off a series of reactions that in turn activates factor XI (antihemolytic factor C or plasma thromboplastin antecedent) then factor IX (antihemolytic factor B or plasma thromboplasmin). In the meantime, chemicals released by the platelets increase the rate of these activation reactions. Finally, factor VIII (antihemolytic factor A) from the platelets and endothelial cells combines with factor IX (antihemolytic factor B or plasma thromboplasmin) to form an enzyme complex that activates factor X (Stuart–Prower factor or thrombokinase), leading to the common pathway. The events in the intrinsic pathway are completed in a few minutes.

Common Pathway

Both the intrinsic and extrinsic pathways lead to the **common pathway**, in which fibrin is produced to seal off the vessel. Once factor X has been activated by either the intrinsic or extrinsic pathway, the enzyme prothrombinase converts factor II, the inactive enzyme prothrombin, into the active enzyme **thrombin**. (Note that if the enzyme thrombin were not normally in an inactive form, clots would form spontaneously, a condition not consistent with life.) Then, thrombin converts factor I, the soluble fibrinogen, into the insoluble fibrin protein strands. Factor XIII then stabilizes the fibrin clot.

Fibrinolysis

The stabilized clot is acted upon by contractile proteins within the platelets. As these proteins contract, they pull on the fibrin threads, bringing the edges of the clot more tightly together, somewhat as we do when tightening loose shoelaces (see [\[link\]](#)^a). This process also wrings out of the clot a small amount of fluid called **serum**, which is blood plasma without its clotting factors.

To restore normal blood flow as the vessel heals, the clot must eventually be removed. **Fibrinolysis** is the gradual degradation of the clot. Again, there is a fairly complicated

series of reactions that involves factor XII and protein-catabolizing enzymes. During this process, the inactive protein plasminogen is converted into the active **plasmin**, which gradually breaks down the fibrin of the clot. Additionally, bradykinin, a vasodilator, is released, reversing the effects of the serotonin and prostaglandins from the platelets. This allows the smooth muscle in the walls of the vessels to relax and helps to restore the circulation.

Plasma Anticoagulants

An **anticoagulant** is any substance that opposes coagulation. Several circulating plasma anticoagulants play a role in limiting the coagulation process to the region of injury and restoring a normal, clot-free condition of blood. For instance, a cluster of proteins collectively referred to as the protein C system inactivates clotting factors involved in the intrinsic pathway. TFPI (tissue factor pathway inhibitor) inhibits the conversion of the inactive factor VII to the active form in the extrinsic pathway. **Antithrombin** inactivates factor X and opposes the conversion of prothrombin (factor II) to thrombin in the common pathway. And as noted earlier, basophils release **heparin**, a short-acting anticoagulant that also opposes prothrombin. Heparin is also found on the surfaces of cells lining the blood vessels. A pharmaceutical form of heparin is often administered therapeutically, for example, in surgical patients at risk for blood clots.

Note:



View these [animations](#) to explore the intrinsic, extrinsic, and common pathways that are involved in the process of coagulation. The coagulation cascade restores hemostasis by activating coagulation factors in the presence of an injury. How does the endothelium of the blood vessel walls prevent the blood from coagulating as it flows through the blood vessels?

Disorders of Clotting

Either an insufficient or an excessive production of platelets can lead to severe disease or death. As discussed earlier, an insufficient number of platelets, called thrombocytopenia, typically results in the inability of blood to form clots. This can lead to excessive bleeding, even from minor wounds.

Another reason for failure of the blood to clot is the inadequate production of functional amounts of one or more clotting factors. This is the case in the genetic disorder **hemophilia**, which is actually a group of related disorders, the most common of which is hemophilia A, accounting for approximately 80 percent of cases. This disorder results in the inability to synthesize sufficient quantities of factor VIII. Hemophilia B is the second most common form, accounting for approximately 20 percent of cases. In this case, there is a deficiency of factor IX. Both of these defects are linked to the X chromosome and are typically passed from a healthy (carrier) mother to her male offspring, since males are XY. Females would need to inherit a defective gene from each parent to manifest the disease, since they are XX. Patients with hemophilia bleed from even minor internal and external wounds, and leak blood into joint spaces after exercise and into urine and stool. Hemophilia C is a rare condition that is triggered by an autosomal (not sex) chromosome that renders factor XI nonfunctional. It is not a true recessive condition, since even individuals with a single copy of the mutant gene show a tendency to bleed. Regular infusions of clotting factors isolated from healthy donors can help prevent bleeding in hemophiliac patients. At some point, genetic therapy will become a viable option.

In contrast to the disorders characterized by coagulation failure is thrombocytosis, also mentioned earlier, a condition characterized by excessive numbers of platelets that increases the risk for excessive clot formation, a condition known as **thrombosis**. A **thrombus** (plural = thrombi) is an aggregation of platelets, erythrocytes, and even WBCs typically trapped within a mass of fibrin strands. While the formation of a clot is normal following the hemostatic mechanism just described, thrombi can form within an intact or only slightly damaged blood vessel. In a large vessel, a thrombus will adhere to the vessel wall and decrease the flow of blood, and is referred to as a mural thrombus. In a small vessel, it may actually totally block the flow of blood and is termed an occlusive thrombus. Thrombi are most commonly caused by vessel damage to the endothelial lining, which activates the clotting mechanism. These may include venous stasis, when blood in the veins, particularly in the legs, remains stationary for long periods. This is one of the dangers of long airplane flights in crowded conditions and may lead to deep vein thrombosis or atherosclerosis, an accumulation of debris in arteries. Thrombophilia, also called hypercoagulation, is a condition in which there is a tendency to form thrombosis. This may be familial (genetic) or acquired. Acquired forms include the autoimmune disease lupus, immune reactions to heparin, polycythemia vera, thrombocytosis, sickle cell disease, pregnancy, and even obesity. A thrombus can seriously impede blood flow to or from

a region and will cause a local increase in blood pressure. If flow is to be maintained, the heart will need to generate a greater pressure to overcome the resistance.

When a portion of a thrombus breaks free from the vessel wall and enters the circulation, it is referred to as an **embolus**. An embolus that is carried through the bloodstream can be large enough to block a vessel critical to a major organ. When it becomes trapped, an embolus is called an embolism. In the heart, brain, or lungs, an embolism may accordingly cause a heart attack, a stroke, or a pulmonary embolism. These are medical emergencies.

Among the many known biochemical activities of aspirin is its role as an anticoagulant. Aspirin (acetylsalicylic acid) is very effective at inhibiting the aggregation of platelets. It is routinely administered during a heart attack or stroke to reduce the adverse effects. Physicians sometimes recommend that patients at risk for cardiovascular disease take a low dose of aspirin on a daily basis as a preventive measure. However, aspirin can also lead to serious side effects, including increasing the risk of ulcers. A patient is well advised to consult a physician before beginning any aspirin regimen.

A class of drugs collectively known as thrombolytic agents can help speed up the degradation of an abnormal clot. If a thrombolytic agent is administered to a patient within 3 hours following a thrombotic stroke, the patient's prognosis improves significantly. However, some strokes are not caused by thrombi, but by hemorrhage. Thus, the cause must be determined before treatment begins. Tissue plasminogen activator is an enzyme that catalyzes the conversion of plasminogen to plasmin, the primary enzyme that breaks down clots. It is released naturally by endothelial cells but is also used in clinical medicine. New research is progressing using compounds isolated from the venom of some species of snakes, particularly vipers and cobras, which may eventually have therapeutic value as thrombolytic agents.

Chapter Review

Hemostasis is the physiological process by which bleeding ceases. Hemostasis involves three basic steps: vascular spasm, the formation of a platelet plug, and coagulation, in which clotting factors promote the formation of a fibrin clot.

Fibrinolysis is the process in which a clot is degraded in a healing vessel.

Anticoagulants are substances that oppose coagulation. They are important in limiting the extent and duration of clotting. Inadequate clotting can result from too few platelets, or inadequate production of clotting factors, for instance, in the genetic disorder hemophilia. Excessive clotting, called thrombosis, can be caused by excessive numbers of platelets. A thrombus is a collection of fibrin, platelets, and erythrocytes that has accumulated along the lining of a blood vessel, whereas an

embolus is a thrombus that has broken free from the vessel wall and is circulating in the bloodstream.

Interactive Link Questions

Exercise:

Problem:

View these [animations](#) to explore the intrinsic, extrinsic, and common pathways that are involved in the process of coagulation. The coagulation cascade restores hemostasis by activating coagulation factors in the presence of an injury. How does the endothelium of the blood vessel walls prevent the blood from coagulating as it flows through the blood vessels?

Solution:

Clotting factors flow through the blood vessels in their inactive state. The endothelium does not have thrombogenic tissue factor to activate clotting factors.

Review Questions

Exercise:

Problem: The first step in hemostasis is _____.

- a. vascular spasm
 - b. conversion of fibrinogen to fibrin
 - c. activation of the intrinsic pathway
 - d. activation of the common pathway
-

Solution:

A

Exercise:

Problem: Prothrombin is converted to thrombin during the _____.

- a. intrinsic pathway
- b. extrinsic pathway

- c. common pathway
- d. formation of the platelet plug

Solution:

C

Exercise:

Problem: Hemophilia is characterized by _____.

- a. inadequate production of heparin
- b. inadequate production of clotting factors
- c. excessive production of fibrinogen
- d. excessive production of platelets

Solution:

B

Critical Thinking Questions

Exercise:

Problem:

A lab technician collects a blood sample in a glass tube. After about an hour, she harvests serum to continue her blood analysis. Explain what has happened during the hour that the sample was in the glass tube.

Solution:

When blood contacts glass, the intrinsic coagulation pathway is initiated. This leads to the common pathway, and the blood clots. Within about 30 minutes, the clot begins to shrink. After an hour, it is about half its original size. Its heavier weight will cause it to fall to the bottom of the tube during centrifugation, allowing the lab technician to harvest the serum remaining at the top.

Exercise:

Problem:

Explain why administration of a thrombolytic agent is a first intervention for someone who has suffered a thrombotic stroke.

Solution:

In a thrombotic stroke, a blood vessel to the brain has been blocked by a thrombus, an aggregation of platelets and erythrocytes within a blood vessel. A thrombolytic agent is a medication that promotes the breakup of thrombi.

Glossary

anticoagulant

substance such as heparin that opposes coagulation

antithrombin

anticoagulant that inactivates factor X and opposes the conversion of prothrombin (factor II) into thrombin in the common pathway

clotting factors

group of 12 identified substances active in coagulation

coagulation

formation of a blood clot; part of the process of hemostasis

common pathway

final coagulation pathway activated either by the intrinsic or the extrinsic pathway, and ending in the formation of a blood clot

embolus

thrombus that has broken free from the blood vessel wall and entered the circulation

extrinsic pathway

initial coagulation pathway that begins with tissue damage and results in the activation of the common pathway

fibrin

insoluble, filamentous protein that forms the structure of a blood clot

fibrinolysis

gradual degradation of a blood clot

hemophilia

genetic disorder characterized by inadequate synthesis of clotting factors

hemorrhage

excessive bleeding

hemostasis

physiological process by which bleeding ceases

heparin

short-acting anticoagulant stored in mast cells and released when tissues are injured, opposes prothrombin

intrinsic pathway

initial coagulation pathway that begins with vascular damage or contact with foreign substances, and results in the activation of the common pathway

plasmin

blood protein active in fibrinolysis

platelet plug

accumulation and adhesion of platelets at the site of blood vessel injury

serum

blood plasma that does not contain clotting factors

thrombin

enzyme essential for the final steps in formation of a fibrin clot

thrombosis

excessive clot formation

thrombus

aggregation of fibrin, platelets, and erythrocytes in an intact artery or vein

tissue factor

protein thromboplastin, which initiates the extrinsic pathway when released in response to tissue damage

vascular spasm

initial step in hemostasis, in which the smooth muscle in the walls of the ruptured or damaged blood vessel contracts

Blood Typing

By the end of this section, you will be able to:

- Describe the two basic physiological consequences of transfusion of incompatible blood
- Compare and contrast ABO and Rh blood groups
- Identify which blood groups may be safely transfused into patients with different ABO types
- Discuss the pathophysiology of hemolytic disease of the newborn

Blood transfusions in humans were risky procedures until the discovery of the major human blood groups by Karl Landsteiner, an Austrian biologist and physician, in 1900. Until that point, physicians did not understand that death sometimes followed blood transfusions, when the type of donor blood infused into the patient was incompatible with the patient's own blood. Blood groups are determined by the presence or absence of specific marker molecules on the plasma membranes of erythrocytes. With their discovery, it became possible for the first time to match patient-donor blood types and prevent transfusion reactions and deaths.

Antigens, Antibodies, and Transfusion Reactions

Antigens are substances that the body does not recognize as belonging to the “self” and that therefore trigger a defensive response from the leukocytes of the immune system. (Seek more content for additional information on immunity.) Here, we will focus on the role of immunity in blood transfusion reactions. With RBCs in particular, you may see the antigens referred to as isoantigens or agglutinogens (surface antigens) and the antibodies referred to as isoantibodies or agglutinins. In this chapter, we will use the more common terms antigens and antibodies.

Antigens are generally large proteins, but may include other classes of organic molecules, including carbohydrates, lipids, and nucleic acids. Following an infusion of incompatible blood, erythrocytes with foreign antigens appear in the bloodstream and trigger an immune response. Proteins called antibodies (immunoglobulins), which are produced by certain B lymphocytes called plasma cells, attach to the antigens on the plasma membranes of the infused erythrocytes and cause them to adhere to one another.

- Because the arms of the Y-shaped antibodies attach randomly to more than one nonself erythrocyte surface, they form clumps of erythrocytes. This process is called **agglutination**.

- The clumps of erythrocytes block small blood vessels throughout the body, depriving tissues of oxygen and nutrients.
- As the erythrocyte clumps are degraded, in a process called **hemolysis**, their hemoglobin is released into the bloodstream. This hemoglobin travels to the kidneys, which are responsible for filtration of the blood. However, the load of hemoglobin released can easily overwhelm the kidney's capacity to clear it, and the patient can quickly develop kidney failure.

More than 50 antigens have been identified on erythrocyte membranes, but the most significant in terms of their potential harm to patients are classified in two groups: the ABO blood group and the Rh blood group.

The ABO Blood Group

Although the **ABO blood group** name consists of three letters, ABO blood typing designates the presence or absence of just two antigens, A and B. Both are glycoproteins. People whose erythrocytes have A antigens on their erythrocyte membrane surfaces are designated blood type A, and those whose erythrocytes have B antigens are blood type B. People can also have both A and B antigens on their erythrocytes, in which case they are blood type AB. People with neither A nor B antigens are designated blood type O. ABO blood types are genetically determined.

Normally the body must be exposed to a foreign antigen before an antibody can be produced. This is not the case for the ABO blood group. Individuals with type A blood—without any prior exposure to incompatible blood—have preformed antibodies to the B antigen circulating in their blood plasma. These antibodies, referred to as anti-B antibodies, will cause agglutination and hemolysis if they ever encounter erythrocytes with B antigens. Similarly, an individual with type B blood has pre-formed anti-A antibodies. Individuals with type AB blood, which has both antigens, do not have preformed antibodies to either of these. People with type O blood lack antigens A and B on their erythrocytes, but both anti-A and anti-B antibodies circulate in their blood plasma.

Rh Blood Groups

The **Rh blood group** is classified according to the presence or absence of a second erythrocyte antigen identified as Rh. (It was first discovered in a type of primate known as a rhesus macaque, which is often used in research, because its blood is similar to that of humans.) Although dozens of Rh antigens have been identified,

only one, designated D, is clinically important. Those who have the Rh D antigen present on their erythrocytes—about 85 percent of Americans—are described as Rh positive (Rh⁺) and those who lack it are Rh negative (Rh⁻). Note that the Rh group is distinct from the ABO group, so any individual, no matter their ABO blood type, may have or lack this Rh antigen. When identifying a patient’s blood type, the Rh group is designated by adding the word positive or negative to the ABO type. For example, A positive (A⁺) means ABO group A blood with the Rh antigen present, and AB negative (AB⁻) means ABO group AB blood without the Rh antigen.

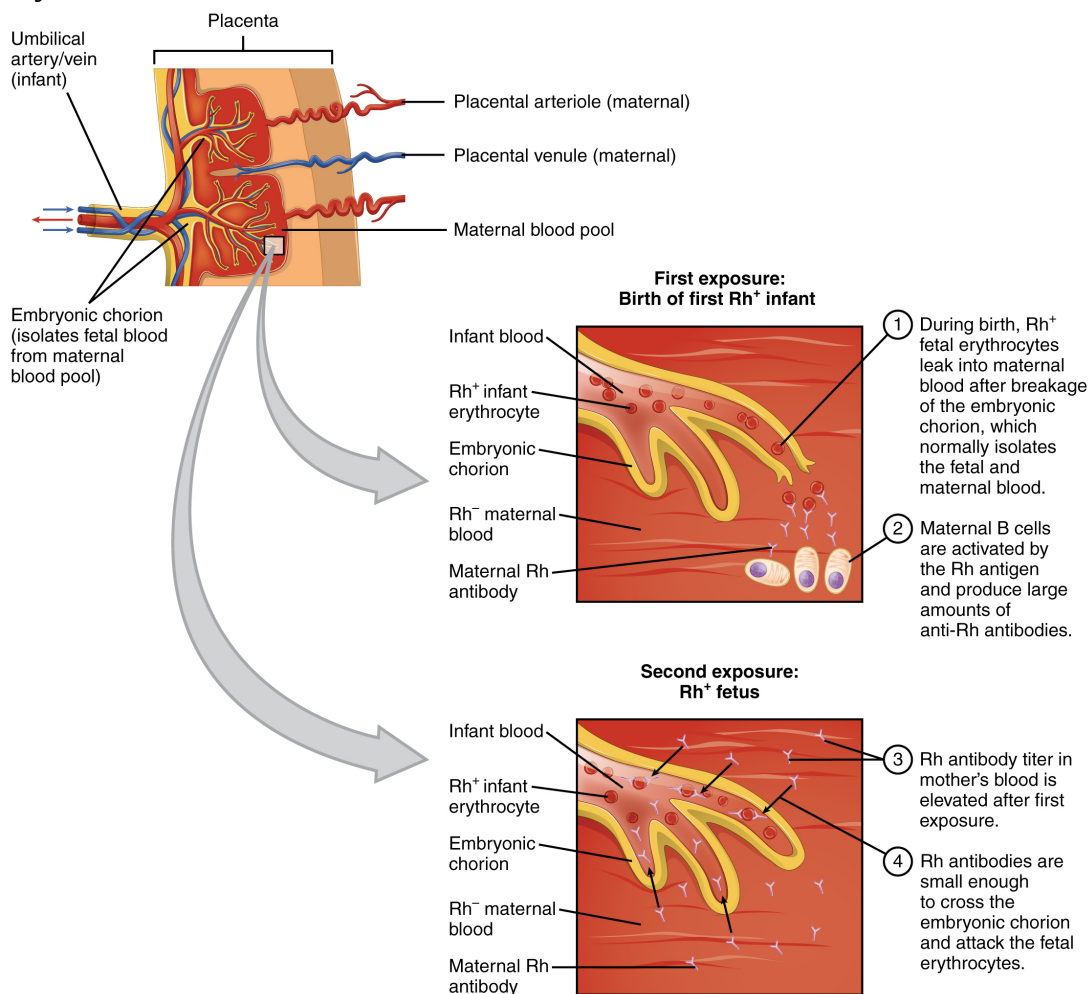
[\[link\]](#) summarizes the distribution of the ABO and Rh blood types within the United States.

| Summary of ABO and Rh Blood Types within the United States | | | | |
|--|-------------------|-----------------|---------------------|-------------------------|
| Blood Type | African-Americans | Asian-Americans | Caucasian-Americans | Latino/Latina-Americans |
| A ⁺ | 24 | 27 | 33 | 29 |
| A ⁻ | 2 | 0.5 | 7 | 2 |
| B ⁺ | 18 | 25 | 9 | 9 |
| B ⁻ | 1 | 0.4 | 2 | 1 |
| AB ⁺ | 4 | 7 | 3 | 2 |
| AB ⁻ | 0.3 | 0.1 | 1 | 0.2 |
| O ⁺ | 47 | 39 | 37 | 53 |
| O ⁻ | 4 | 1 | 8 | 4 |

In contrast to the ABO group antibodies, which are preformed, antibodies to the Rh antigen are produced only in Rh⁻ individuals after exposure to the antigen. This

process, called sensitization, occurs following a transfusion with Rh-incompatible blood or, more commonly, with the birth of an Rh⁺ baby to an Rh⁻ mother. Problems are rare in a first pregnancy, since the baby's Rh⁺ cells rarely cross the placenta (the organ of gas and nutrient exchange between the baby and the mother). However, during or immediately after birth, the Rh⁻ mother can be exposed to the baby's Rh⁺ cells ([\[link\]](#)). Research has shown that this occurs in about 13–14 percent of such pregnancies. After exposure, the mother's immune system begins to generate anti-Rh antibodies. If the mother should then conceive another Rh⁺ baby, the Rh antibodies she has produced can cross the placenta into the fetal bloodstream and destroy the fetal RBCs. This condition, known as **hemolytic disease of the newborn (HDN)** or erythroblastosis fetalis, may cause anemia in mild cases, but the agglutination and hemolysis can be so severe that without treatment the fetus may die in the womb or shortly after birth.

Erythroblastosis Fetalis



The first exposure of an Rh⁻ mother to Rh⁺ erythrocytes during pregnancy induces sensitization. Anti-Rh antibodies begin to

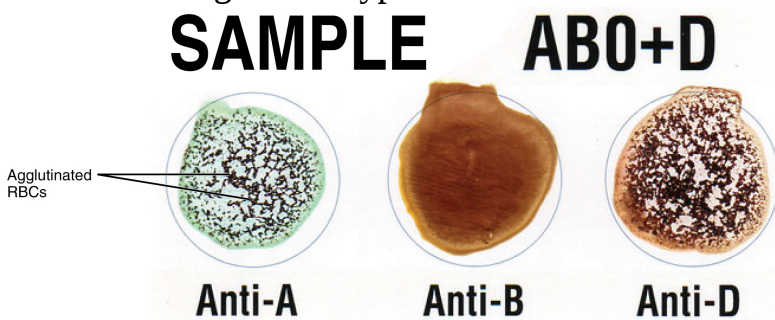
circulate in the mother's bloodstream. A second exposure occurs with a subsequent pregnancy with an Rh⁺ fetus in the uterus. Maternal anti-Rh antibodies may cross the placenta and enter the fetal bloodstream, causing agglutination and hemolysis of fetal erythrocytes.

A drug known as RhoGAM, short for Rh immune globulin, can temporarily prevent the development of Rh antibodies in the Rh⁻ mother, thereby averting this potentially serious disease for the fetus. RhoGAM antibodies destroy any fetal Rh⁺ erythrocytes that may cross the placental barrier. RhoGAM is normally administered to Rh⁻ mothers during weeks 26–28 of pregnancy and within 72 hours following birth. It has proven remarkably effective in decreasing the incidence of HDN. Earlier we noted that the incidence of HDN in an Rh⁺ subsequent pregnancy to an Rh⁻ mother is about 13–14 percent without preventive treatment. Since the introduction of RhoGAM in 1968, the incidence has dropped to about 0.1 percent in the United States.

Determining ABO Blood Types

Clinicians are able to determine a patient's blood type quickly and easily using commercially prepared antibodies. An unknown blood sample is allocated into separate wells. Into one well a small amount of anti-A antibody is added, and to another a small amount of anti-B antibody. If the antigen is present, the antibodies will cause visible agglutination of the cells ([\[link\]](#)). The blood should also be tested for Rh antibodies.

Cross Matching Blood Types



This sample of a commercially produced “bedside” card enables quick typing of both a recipient's and donor's blood before transfusion. The card contains three reaction sites or wells.

One is coated with an anti-A antibody, one with an anti-B antibody, and one with an anti-D antibody (tests for the presence of Rh factor D). Mixing a drop of blood and saline into each well enables the blood to interact with a preparation of type-specific antibodies, also called anti-seras. Agglutination of RBCs in a given site indicates a positive identification of the blood antigens, in this case A and Rh antigens for blood type A⁺. For the purpose of transfusion, the donor's and recipient's blood types must match.

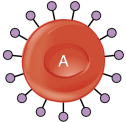
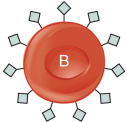
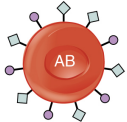
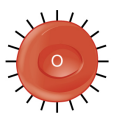






ABO Transfusion Protocols

To avoid transfusion reactions, it is best to transfuse only matching blood types; that is, a type B⁺ recipient should ideally receive blood only from a type B⁺ donor and so on. That said, in emergency situations, when acute hemorrhage threatens the patient's life, there may not be time for cross matching to identify blood type. In these cases, blood from a **universal donor**—an individual with type O⁻ blood—may be transfused. Recall that type O erythrocytes do not display A or B antigens. Thus, anti-A or anti-B antibodies that might be circulating in the patient's blood plasma will not encounter any erythrocyte surface antigens on the donated blood and therefore will not be provoked into a response. One problem with this designation of universal donor is if the O⁻ individual had prior exposure to Rh antigen, Rh antibodies may be present in the donated blood. Also, introducing type O blood into an individual with type A, B, or AB blood will nevertheless introduce antibodies against both A and B antigens, as these are always circulating in the type O blood plasma. This may cause problems for the recipient, but because the volume of blood transfused is much lower than the volume of the patient's own blood, the adverse effects of the relatively few infused plasma antibodies are typically limited. Rh factor also plays a role. If Rh⁻ individuals receiving blood have had prior exposure to Rh antigen, antibodies for this antigen may be present in the blood and trigger agglutination to some degree. Although it is always preferable to cross match a patient's blood before transfusing, in a true life-threatening emergency situation, this is not always possible, and these procedures may be implemented.

A patient with blood type AB⁺ is known as the **universal recipient**. This patient can theoretically receive any type of blood, because the patient’s own blood—having both A and B antigens on the erythrocyte surface—does not produce anti-A or anti-B antibodies. In addition, an Rh⁺ patient can receive both Rh⁺ and Rh⁻ blood. However, keep in mind that the donor’s blood will contain circulating antibodies, again with possible negative implications. [\[link\]](#) summarizes the blood types and compatibilities.

At the scene of multiple-vehicle accidents, military engagements, and natural or human-caused disasters, many victims may suffer simultaneously from acute hemorrhage, yet type O blood may not be immediately available. In these circumstances, medics may at least try to replace some of the volume of blood that has been lost. This is done by intravenous administration of a saline solution that provides fluids and electrolytes in proportions equivalent to those of normal blood plasma. Research is ongoing to develop a safe and effective artificial blood that would carry out the oxygen-carrying function of blood without the RBCs, enabling transfusions in the field without concern for incompatibility. These blood substitutes normally contain hemoglobin- as well as perfluorocarbon-based oxygen carriers.

ABO Blood Group

| Blood Type | | | | |
|--|--|--|---|--|
| | A | B | AB | O |
| Red Blood Cell Type |  |  |  |  |
| Antibodies in Plasma |  Anti-B |  Anti-A | None |  Anti-A and Anti-B |
| Antigens in Red blood Cell |  A antigen |  B antigen |  A and B antigens | None |
| Blood Types Compatible in an Emergency | A, O | B, O | A, B, AB, O (AB ⁺ is the universal recipient) | O (O is the universal donor) |

This chart summarizes the characteristics of the blood types in the ABO blood group. See the text for more on the concept of a universal donor or recipient.

Chapter Review

Antigens are nonself molecules, usually large proteins, which provoke an immune response. In transfusion reactions, antibodies attach to antigens on the surfaces of erythrocytes and cause agglutination and hemolysis. ABO blood group antigens are designated A and B. People with type A blood have A antigens on their erythrocytes, whereas those with type B blood have B antigens. Those with AB blood have both A and B antigens, and those with type O blood have neither A nor B antigens. The blood plasma contains preformed antibodies against the antigens not present on a person's erythrocytes.

A second group of blood antigens is the Rh group, the most important of which is Rh D. People with Rh⁻ blood do not have this antigen on their erythrocytes, whereas those who are Rh⁺ do. About 85 percent of Americans are Rh⁺. When a woman who is Rh⁻ becomes pregnant with an Rh⁺ fetus, her body may begin to produce anti-Rh antibodies. If she subsequently becomes pregnant with a second Rh⁺ fetus and is not treated preventively with RhoGAM, the fetus will be at risk for an antigen-antibody reaction, including agglutination and hemolysis. This is known as hemolytic disease of the newborn.

Cross matching to determine blood type is necessary before transfusing blood, unless the patient is experiencing hemorrhage that is an immediate threat to life, in which case type O⁻ blood may be transfused.

Review Questions

Exercise:

Problem:

The process in which antibodies attach to antigens, causing the formation of masses of linked cells, is called _____.

- a. sensitization
- b. coagulation
- c. agglutination
- d. hemolysis

Solution:

C

Exercise:

Problem: People with ABO blood type O _____.

- a. have both antigens A and B on their erythrocytes
- b. lack both antigens A and B on their erythrocytes
- c. have neither anti-A nor anti-B antibodies circulating in their blood plasma
- d. are considered universal recipients

Solution:

B

Exercise:

Problem:

Hemolytic disease of the newborn is a risk during a subsequent pregnancy in which _____.

- a. a type AB mother is carrying a type O fetus
- b. a type O mother is carrying a type AB fetus
- c. an Rh⁺ mother is carrying an Rh⁻ fetus
- d. an Rh⁻ mother is carrying a second Rh⁺ fetus

Solution:

D

Critical Thinking Questions**Exercise:**

Problem:

Following a motor vehicle accident, a patient is rushed to the emergency department with multiple traumatic injuries, causing severe bleeding. The patient's condition is critical, and there is no time for determining his blood type. What type of blood is transfused, and why?

Solution:

In emergency situations, blood type O⁻ will be infused until cross matching can be done. Blood type O⁻ is called the universal donor blood because the erythrocytes have neither A nor B antigens on their surface, and the Rh factor is negative.

Exercise:**Problem:**

In preparation for a scheduled surgery, a patient visits the hospital lab for a blood draw. The technician collects a blood sample and performs a test to determine its type. She places a sample of the patient's blood in two wells. To the first well she adds anti-A antibody. To the second she adds anti-B antibody. Both samples visibly agglutinate. Has the technician made an error, or is this a normal response? If normal, what blood type does this indicate?

Solution:

The lab technician has not made an error. Blood type AB has both A and B surface antigens, and neither anti-A nor anti-B antibodies circulating in the plasma. When anti-A antibodies (added to the first well) contact A antigens on AB erythrocytes, they will cause agglutination. Similarly, when anti-B antibodies contact B antigens on AB erythrocytes, they will cause agglutination.

References

American Red Cross (US). Blood types [Internet]. c2013 [cited 2013 Apr 3]. Available from: <http://www.redcrossblood.org/learn-about-blood/blood-types> 2013

Glossary**ABO blood group**

blood-type classification based on the presence or absence of A and B glycoproteins on the erythrocyte membrane surface

agglutination

clustering of cells into masses linked by antibodies

cross matching

blood test for identification of blood type using antibodies and small samples of blood

hemolysis

destruction (lysis) of erythrocytes and the release of their hemoglobin into circulation

hemolytic disease of the newborn (HDN)

(also, erythroblastosis fetalis) disorder causing agglutination and hemolysis in an Rh^+ fetus or newborn of an Rh^- mother

Rh blood group

blood-type classification based on the presence or absence of the antigen Rh on the erythrocyte membrane surface

universal donor

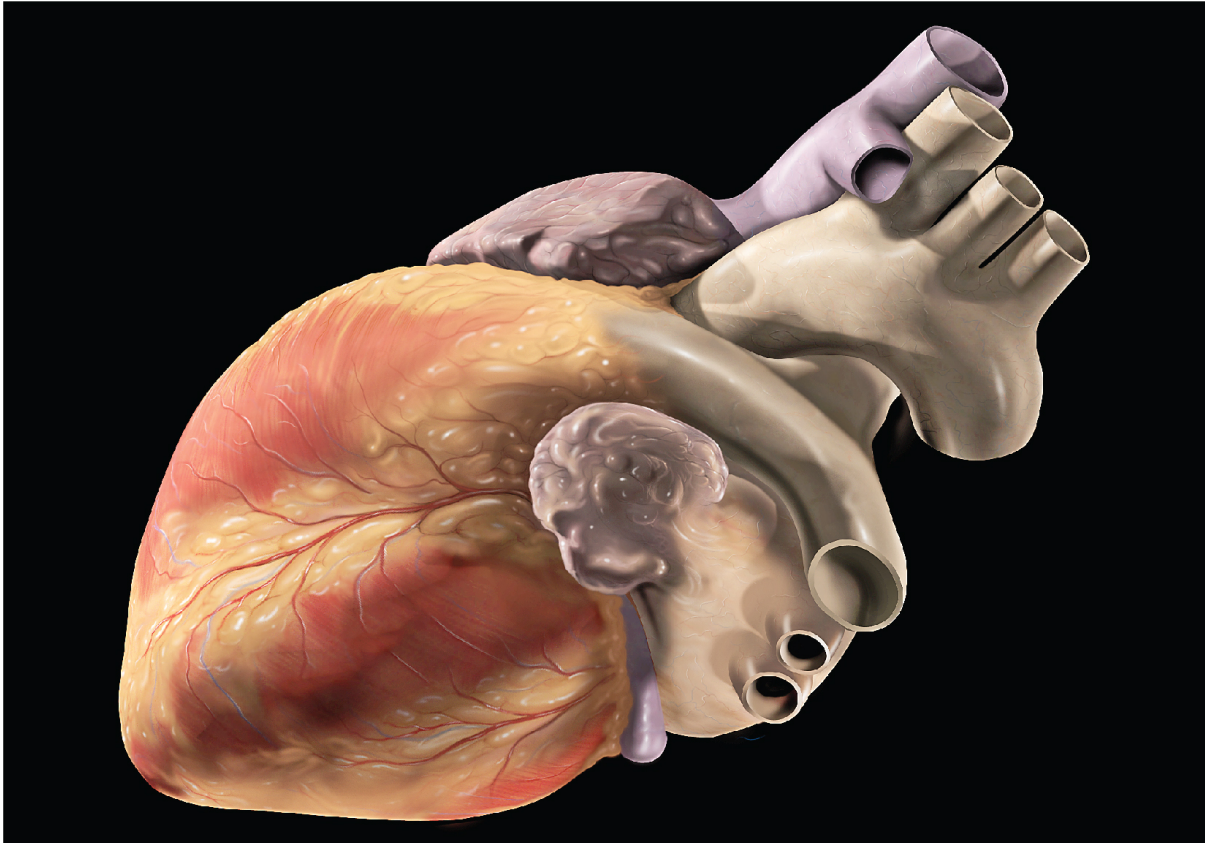
individual with type O^- blood

universal recipient

individual with type AB^+ blood

Introduction
class="introduction"
Human Heart

This artist's
conception
of the human
heart
suggests a
powerful
engine—not
inappropriate for a
muscular
pump that
keeps the
body
continually
supplied
with blood.
(credit:
Patrick J.
Lynch)



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Identify and describe the interior and exterior parts of the human heart
- Describe the path of blood through the cardiac circuits
- Describe the size, shape, and location of the heart
- Compare cardiac muscle to skeletal and smooth muscle
- Explain the cardiac conduction system
- Describe the process and purpose of an electrocardiogram
- Explain the cardiac cycle
- Calculate cardiac output
- Describe the effects of exercise on cardiac output and heart rate
- Name the centers of the brain that control heart rate and describe their function
- Identify other factors affecting heart rate

- Describe fetal heart development

In this chapter, you will explore the remarkable pump that propels the blood into the vessels. There is no single better word to describe the function of the heart other than “pump,” since its contraction develops the pressure that ejects blood into the major vessels: the aorta and pulmonary trunk. From these vessels, the blood is distributed to the remainder of the body.

Although the connotation of the term “pump” suggests a mechanical device made of steel and plastic, the anatomical structure is a living, sophisticated muscle. As you read this chapter, try to keep these twin concepts in mind: pump and muscle.

Although the term “heart” is an English word, cardiac (heart-related) terminology can be traced back to the Latin term, “kardia.” Cardiology is the study of the heart, and cardiologists are the physicians who deal primarily with the heart.

Heart Anatomy

By the end of this section, you will be able to:

- Describe the location and position of the heart within the body cavity
- Describe the internal and external anatomy of the heart
- Identify the tissue layers of the heart
- Relate the structure of the heart to its function as a pump
- Compare systemic circulation to pulmonary circulation
- Identify the veins and arteries of the coronary circulation system
- Trace the pathway of oxygenated and deoxygenated blood thorough the chambers of the heart

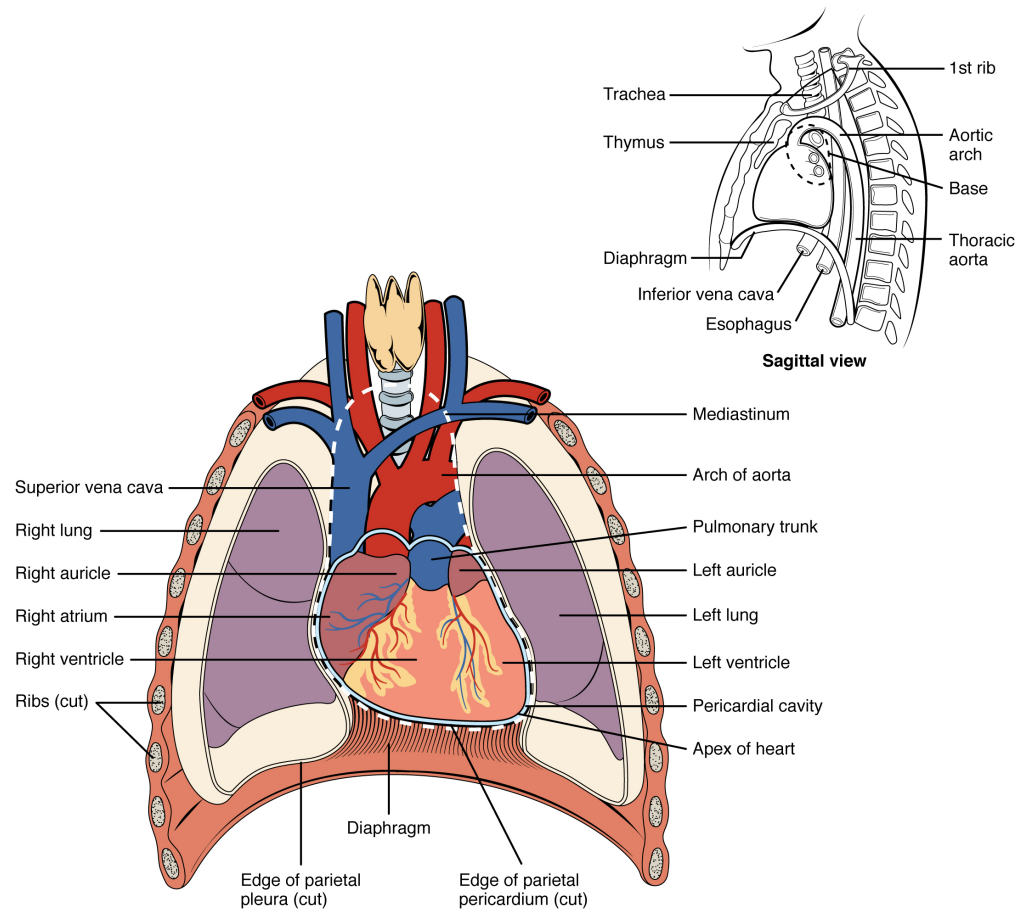
The vital importance of the heart is obvious. If one assumes an average rate of contraction of 75 contractions per minute, a human heart would contract approximately 108,000 times in one day, more than 39 million times in one year, and nearly 3 billion times during a 75-year lifespan. Each of the major pumping chambers of the heart ejects approximately 70 mL blood per contraction in a resting adult. This would be equal to 5.25 liters of fluid per minute and approximately 14,000 liters per day. Over one year, that would equal 10,000,000 liters or 2.6 million gallons of blood sent through roughly 60,000 miles of vessels. In order to understand how that happens, it is necessary to understand the anatomy and physiology of the heart.

Location of the Heart

The human heart is located within the thoracic cavity, medially between the lungs in the space known as the mediastinum. [\[link\]](#) shows the position of the heart within the thoracic cavity. Within the mediastinum, the heart is separated from the other mediastinal structures by a tough membrane known as the pericardium, or pericardial sac, and sits in its own space called the **pericardial cavity**. The dorsal surface of the heart lies near the bodies of the vertebrae, and its anterior surface sits deep to the sternum and costal cartilages. The great veins, the superior and inferior venae cavae, and the great arteries, the aorta and pulmonary trunk, are attached to the superior surface of the heart, called the base. The base of the heart is located at the level of the third costal cartilage, as seen in [\[link\]](#). The inferior tip of the heart, the apex, lies just to the left of the sternum between

the junction of the fourth and fifth ribs near their articulation with the costal cartilages. The right side of the heart is deflected anteriorly, and the left side is deflected posteriorly. It is important to remember the position and orientation of the heart when placing a stethoscope on the chest of a patient and listening for heart sounds, and also when looking at images taken from a midsagittal perspective. The slight deviation of the apex to the left is reflected in a depression in the medial surface of the inferior lobe of the left lung, called the **cardiac notch**.

Position of the Heart in the Thorax



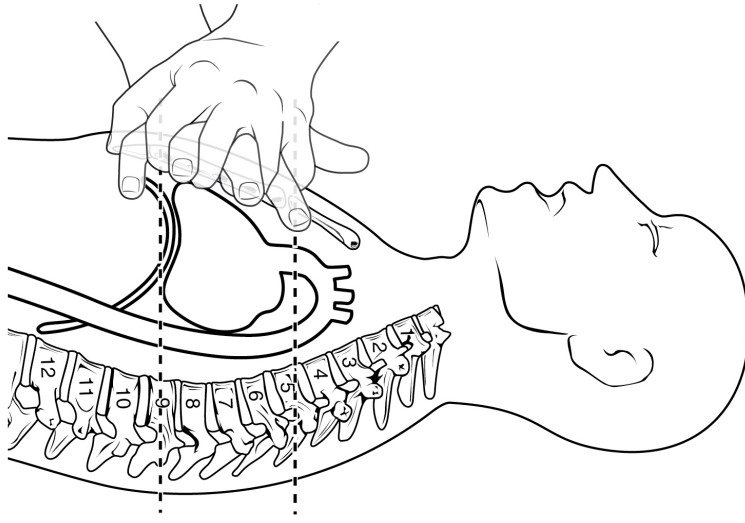
The heart is located within the thoracic cavity, medially between the lungs in the mediastinum. It is about the size of a fist, is broad at the top, and tapers toward the base.

Note:**Everyday Connection****CPR**

The position of the heart in the torso between the vertebrae and sternum (see [\[link\]](#) for the position of the heart within the thorax) allows for individuals to apply an emergency technique known as cardiopulmonary resuscitation (CPR) if the heart of a patient should stop. By applying pressure with the flat portion of one hand on the sternum in the area between the line at T4 and T9 ([\[link\]](#)), it is possible to manually compress the blood within the heart enough to push some of the blood within it into the pulmonary and systemic circuits. This is particularly critical for the brain, as irreversible damage and death of neurons occur within minutes of loss of blood flow. Current standards call for compression of the chest at least 5 cm deep and at a rate of 100 compressions per minute, a rate equal to the beat in “Staying Alive,” recorded in 1977 by the Bee Gees. If you are unfamiliar with this song, a version is available on www.youtube.com. At this stage, the emphasis is on performing high-quality chest compressions, rather than providing artificial respiration. CPR is generally performed until the patient regains spontaneous contraction or is declared dead by an experienced healthcare professional.

When performed by untrained or overzealous individuals, CPR can result in broken ribs or a broken sternum, and can inflict additional severe damage on the patient. It is also possible, if the hands are placed too low on the sternum, to manually drive the xiphoid process into the liver, a consequence that may prove fatal for the patient. Proper training is essential. This proven life-sustaining technique is so valuable that virtually all medical personnel as well as concerned members of the public should be certified and routinely recertified in its application. CPR courses are offered at a variety of locations, including colleges, hospitals, the American Red Cross, and some commercial companies. They normally include practice of the compression technique on a mannequin.

CPR Technique



If the heart should stop, CPR can maintain the flow of blood until the heart resumes beating. By applying pressure to the sternum, the blood within the heart will be squeezed out of the heart and into the circulation. Proper positioning of the hands on the sternum to perform CPR would be between the lines at T4 and T9.

Note:



Visit the American Heart Association [website](#) to help locate a course near your home in the United States. There are also many other national and

regional heart associations that offer the same service, depending upon the location.

Shape and Size of the Heart

The shape of the heart is similar to a pinecone, rather broad at the superior surface and tapering to the apex (see [\[link\]](#)). A typical heart is approximately the size of your fist: 12 cm (5 in) in length, 8 cm (3.5 in) wide, and 6 cm (2.5 in) in thickness. Given the size difference between most members of the sexes, the weight of a female heart is approximately 250–300 grams (9 to 11 ounces), and the weight of a male heart is approximately 300–350 grams (11 to 12 ounces). The heart of a well-trained athlete, especially one specializing in aerobic sports, can be considerably larger than this. Cardiac muscle responds to exercise in a manner similar to that of skeletal muscle. That is, exercise results in the addition of protein myofilaments that increase the size of the individual cells without increasing their numbers, a concept called hypertrophy. Hearts of athletes can pump blood more effectively at lower rates than those of nonathletes. Enlarged hearts are not always a result of exercise; they can result from pathologies, such as **hypertrophic cardiomyopathy**. The cause of an abnormally enlarged heart muscle is unknown, but the condition is often undiagnosed and can cause sudden death in apparently otherwise healthy young people.

Chambers and Circulation through the Heart

The human heart consists of four chambers: The left side and the right side each have one **atrium** and one **ventricle**. Each of the upper chambers, the right atrium (plural = atria) and the left atrium, acts as a receiving chamber and contracts to push blood into the lower chambers, the right ventricle and the left ventricle. The ventricles serve as the primary pumping chambers of the heart, propelling blood to the lungs or to the rest of the body.

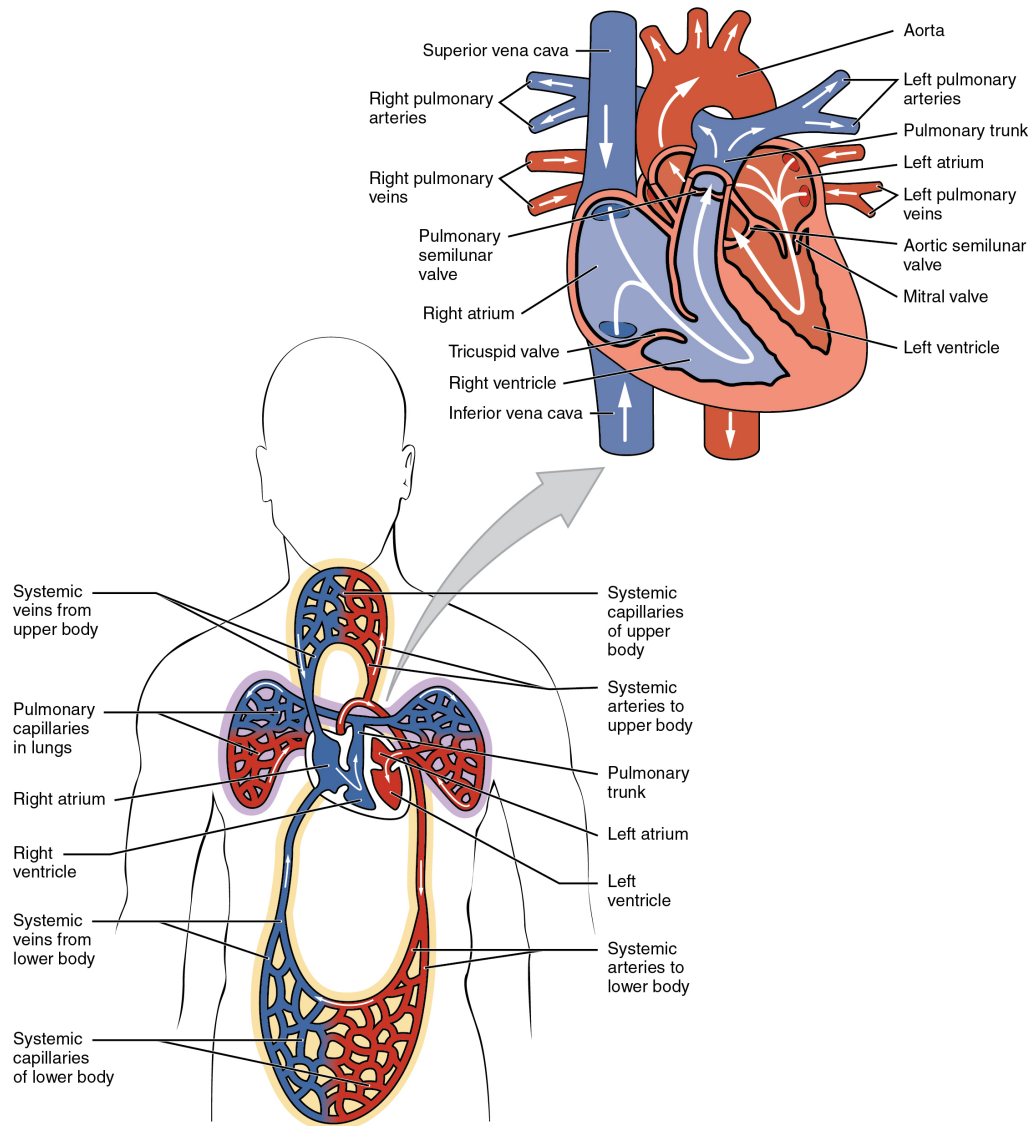
There are two distinct but linked circuits in the human circulation called the pulmonary and systemic circuits. Although both circuits transport blood and

everything it carries, we can initially view the circuits from the point of view of gases. The **pulmonary circuit** transports blood to and from the lungs, where it picks up oxygen and delivers carbon dioxide for exhalation. The **systemic circuit** transports oxygenated blood to virtually all of the tissues of the body and returns relatively deoxygenated blood and carbon dioxide to the heart to be sent back to the pulmonary circulation.

The right ventricle pumps deoxygenated blood into the **pulmonary trunk**, which leads toward the lungs and bifurcates into the left and right **pulmonary arteries**. These vessels in turn branch many times before reaching the **pulmonary capillaries**, where gas exchange occurs: Carbon dioxide exits the blood and oxygen enters. The pulmonary trunk arteries and their branches are the only arteries in the post-natal body that carry relatively deoxygenated blood. Highly oxygenated blood returning from the pulmonary capillaries in the lungs passes through a series of vessels that join together to form the **pulmonary veins**—the only post-natal veins in the body that carry highly oxygenated blood. The pulmonary veins conduct blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and on to the many branches of the systemic circuit. Eventually, these vessels will lead to the systemic capillaries, where exchange with the tissue fluid and cells of the body occurs. In this case, oxygen and nutrients exit the systemic capillaries to be used by the cells in their metabolic processes, and carbon dioxide and waste products will enter the blood.

The blood exiting the systemic capillaries is lower in oxygen concentration than when it entered. The capillaries will ultimately unite to form venules, joining to form ever-larger veins, eventually flowing into the two major systemic veins, the **superior vena cava** and the **inferior vena cava**, which return blood to the right atrium. The blood in the superior and inferior venae cavae flows into the right atrium, which pumps blood into the right ventricle. This process of blood circulation continues as long as the individual remains alive. Understanding the flow of blood through the pulmonary and systemic circuits is critical to all health professions ([\[link\]](#)).

Dual System of the Human Blood Circulation



Blood flows from the right atrium to the right ventricle, where it is pumped into the pulmonary circuit. The blood in the pulmonary artery branches is low in oxygen but relatively high in carbon dioxide. Gas exchange occurs in the pulmonary capillaries (oxygen into the blood, carbon dioxide out), and blood high in oxygen and low in carbon dioxide is returned to the left atrium. From here, blood enters the left ventricle, which pumps it into the systemic circuit. Following exchange in the systemic capillaries (oxygen and nutrients out of the capillaries and carbon

dioxide and wastes in), blood returns to the right atrium and the cycle is repeated.

Membranes, Surface Features, and Layers

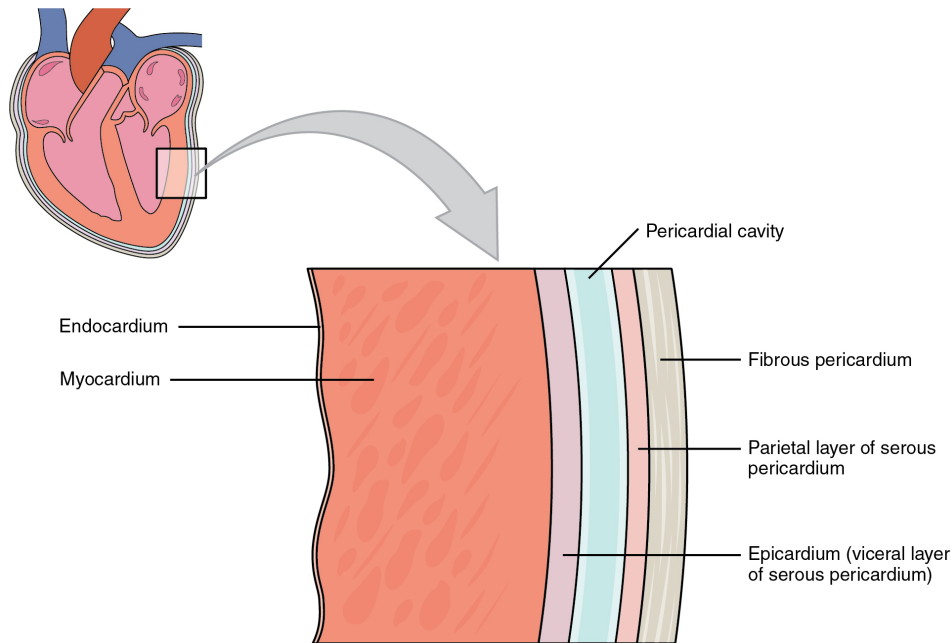
Our exploration of more in-depth heart structures begins by examining the membrane that surrounds the heart, the prominent surface features of the heart, and the layers that form the wall of the heart. Each of these components plays its own unique role in terms of function.

Membranes

The membrane that directly surrounds the heart and defines the pericardial cavity is called the **pericardium** or **pericardial sac**. It also surrounds the “roots” of the major vessels, or the areas of closest proximity to the heart. The pericardium, which literally translates as “around the heart,” consists of two distinct sublayers: the sturdy outer fibrous pericardium and the inner serous pericardium. The fibrous pericardium is made of tough, dense connective tissue that protects the heart and maintains its position in the thorax. The more delicate serous pericardium consists of two layers: the parietal pericardium, which is fused to the fibrous pericardium, and an inner visceral pericardium, or **epicardium**, which is fused to the heart and is part of the heart wall. The pericardial cavity, filled with lubricating serous fluid, lies between the epicardium and the pericardium.

In most organs within the body, visceral serous membranes such as the epicardium are microscopic. However, in the case of the heart, it is not a microscopic layer but rather a macroscopic layer, consisting of a simple squamous epithelium called a **mesothelium**, reinforced with loose, irregular, or areolar connective tissue that attaches to the pericardium. This mesothelium secretes the lubricating serous fluid that fills the pericardial cavity and reduces friction as the heart contracts. [\[link\]](#) illustrates the pericardial membrane and the layers of the heart.

Pericardial Membranes and Layers of the Heart Wall



The pericardial membrane that surrounds the heart consists of three layers and the pericardial cavity. The heart wall also consists of three layers. The pericardial membrane and the heart wall share the epicardium.

Note:

Disorders of the...

Heart: Cardiac Tamponade

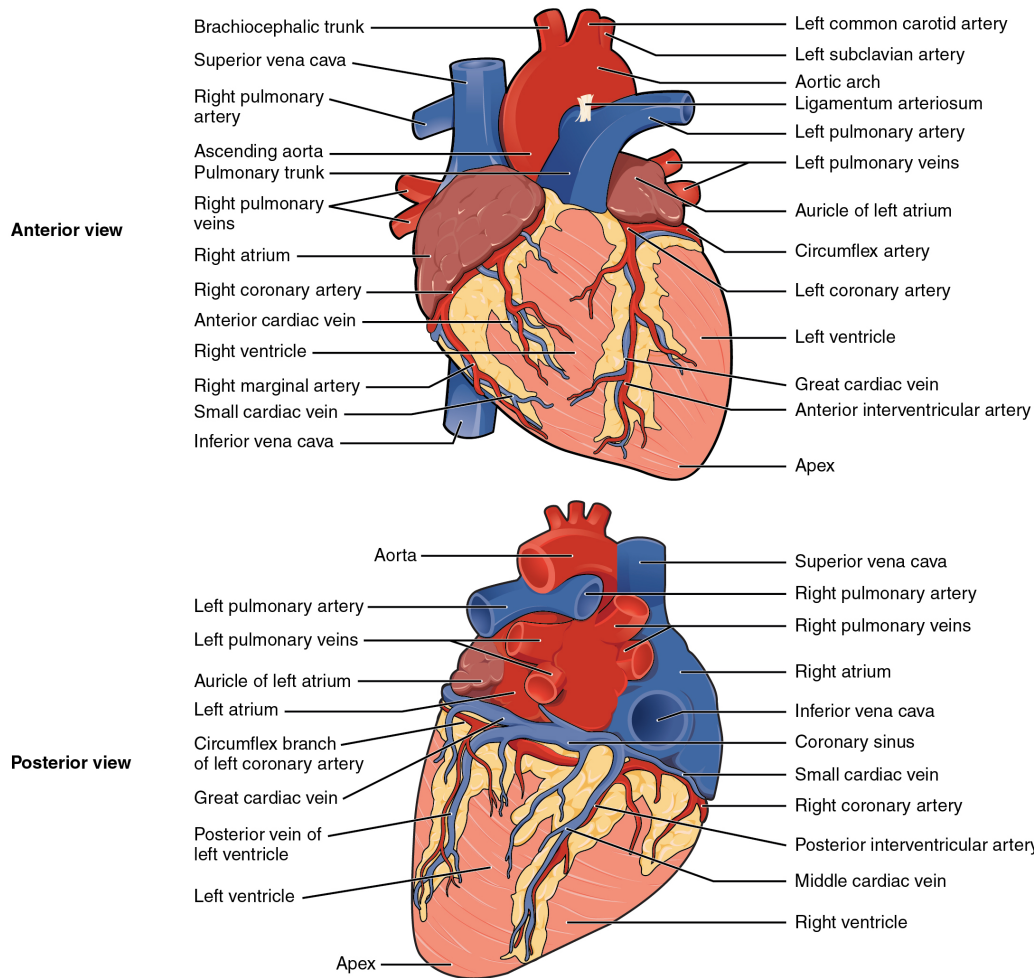
If excess fluid builds within the pericardial space, it can lead to a condition called cardiac tamponade, or pericardial tamponade. With each contraction of the heart, more fluid—in most instances, blood—accumulates within the pericardial cavity. In order to fill with blood for the next contraction, the heart must relax. However, the excess fluid in the pericardial cavity puts pressure on the heart and prevents full relaxation, so the chambers within the heart contain slightly less blood as they begin each heart cycle. Over time, less and less blood is ejected from the heart. If the fluid builds up slowly, as in hypothyroidism, the pericardial cavity may be able to expand gradually to accommodate this extra volume. Some cases of fluid in excess

of one liter within the pericardial cavity have been reported. Rapid accumulation of as little as 100 mL of fluid following trauma may trigger cardiac tamponade. Other common causes include myocardial rupture, pericarditis, cancer, or even cardiac surgery. Removal of this excess fluid requires insertion of drainage tubes into the pericardial cavity. Premature removal of these drainage tubes, for example, following cardiac surgery, or clot formation within these tubes are causes of this condition. Untreated, cardiac tamponade can lead to death.

Surface Features of the Heart

Inside the pericardium, the surface features of the heart are visible, including the four chambers. There is a superficial leaf-like extension of the atria near the superior surface of the heart, one on each side, called an **auricle**—a name that means “ear like”—because its shape resembles the external ear of a human ([\[link\]](#)). Auricles are relatively thin-walled structures that can fill with blood and empty into the atria or upper chambers of the heart. You may also hear them referred to as atrial appendages. Also prominent is a series of fat-filled grooves, each of which is known as a **sulcus** (plural = sulci), along the superior surfaces of the heart. Major coronary blood vessels are located in these sulci. The deep **coronary sulcus** is located between the atria and ventricles. Located between the left and right ventricles are two additional sulci that are not as deep as the coronary sulcus. The **anterior interventricular sulcus** is visible on the anterior surface of the heart, whereas the **posterior interventricular sulcus** is visible on the posterior surface of the heart. [\[link\]](#) illustrates anterior and posterior views of the surface of the heart.

External Anatomy of the Heart



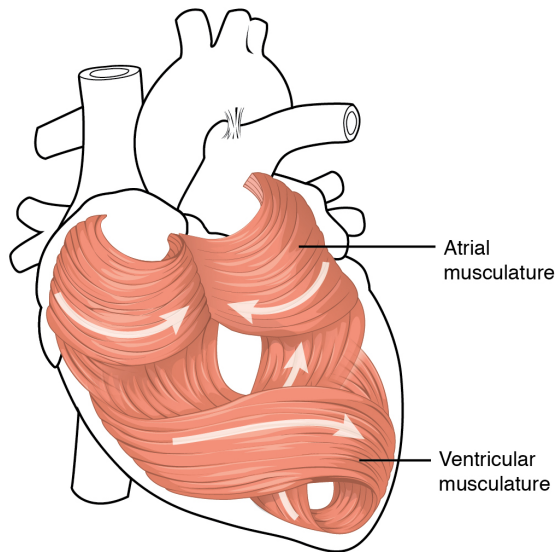
Inside the pericardium, the surface features of the heart are visible.

Layers

The wall of the heart is composed of three layers of unequal thickness. From superficial to deep, these are the epicardium, the myocardium, and the endocardium (see [\[link\]](#)). The outermost layer of the wall of the heart is also the innermost layer of the pericardium, the epicardium, or the visceral pericardium discussed earlier.

The middle and thickest layer is the **myocardium**, made largely of cardiac muscle cells. It is built upon a framework of collagenous fibers, plus the blood vessels that supply the myocardium and the nerve fibers that help regulate the heart. It is the contraction of the myocardium that pumps blood through the heart and into the major arteries. The muscle pattern is elegant and complex, as the muscle cells swirl and spiral around the chambers of the heart. They form a figure 8 pattern around the atria and around the bases of the great vessels. Deeper ventricular muscles also form a figure 8 around the two ventricles and proceed toward the apex. More superficial layers of ventricular muscle wrap around both ventricles. This complex swirling pattern allows the heart to pump blood more effectively than a simple linear pattern would. [\[link\]](#) illustrates the arrangement of muscle cells.

Heart Musculature

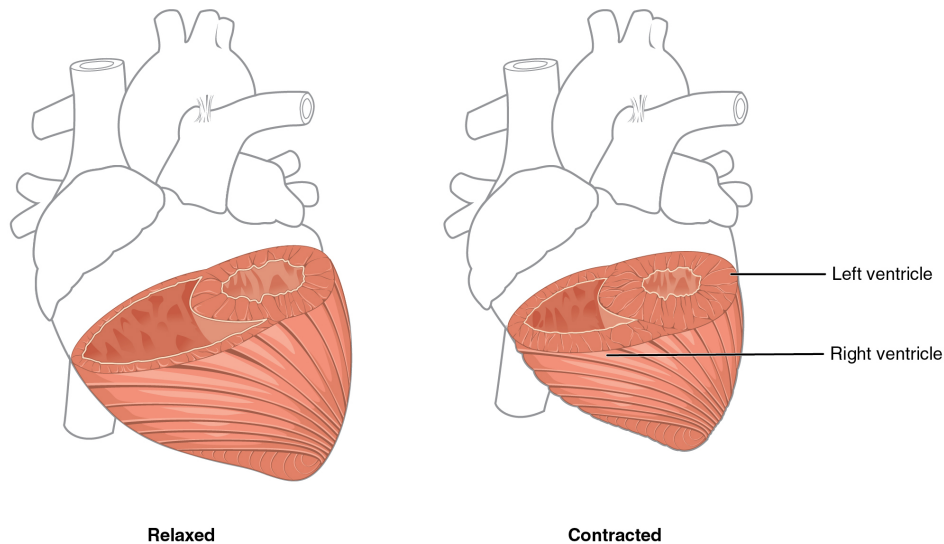


The swirling pattern of cardiac muscle tissue contributes significantly to the heart's ability to pump blood effectively.

Although the ventricles on the right and left sides pump the same amount of blood per contraction, the muscle of the left ventricle is much thicker and better developed than that of the right ventricle. In order to overcome the

high resistance required to pump blood into the long systemic circuit, the left ventricle must generate a great amount of pressure. The right ventricle does not need to generate as much pressure, since the pulmonary circuit is shorter and provides less resistance. [\[link\]](#) illustrates the differences in muscular thickness needed for each of the ventricles.

Differences in Ventricular Muscle Thickness



The myocardium in the left ventricle is significantly thicker than that of the right ventricle. Both ventricles pump the same amount of blood, but the left ventricle must generate a much greater pressure to overcome greater resistance in the systemic circuit. The ventricles are shown in both relaxed and contracting states. Note the differences in the relative size of the lumens, the region inside each ventricle where the blood is contained.

The innermost layer of the heart wall, the **endocardium**, is joined to the myocardium with a thin layer of connective tissue. The endocardium lines the chambers where the blood circulates and covers the heart valves. It is made of simple squamous epithelium called **endothelium**, which is continuous with the endothelial lining of the blood vessels (see [\[link\]](#)).

Once regarded as a simple lining layer, recent evidence indicates that the endothelium of the endocardium and the coronary capillaries may play active roles in regulating the contraction of the muscle within the myocardium. The endothelium may also regulate the growth patterns of the cardiac muscle cells throughout life, and the endothelins it secretes create an environment in the surrounding tissue fluids that regulates ionic concentrations and states of contractility. Endothelins are potent vasoconstrictors and, in a normal individual, establish a homeostatic balance with other vasoconstrictors and vasodilators.

Internal Structure of the Heart

Recall that the heart's contraction cycle follows a dual pattern of circulation—the pulmonary and systemic circuits—because of the pairs of chambers that pump blood into the circulation. In order to develop a more precise understanding of cardiac function, it is first necessary to explore the internal anatomical structures in more detail.

Septa of the Heart

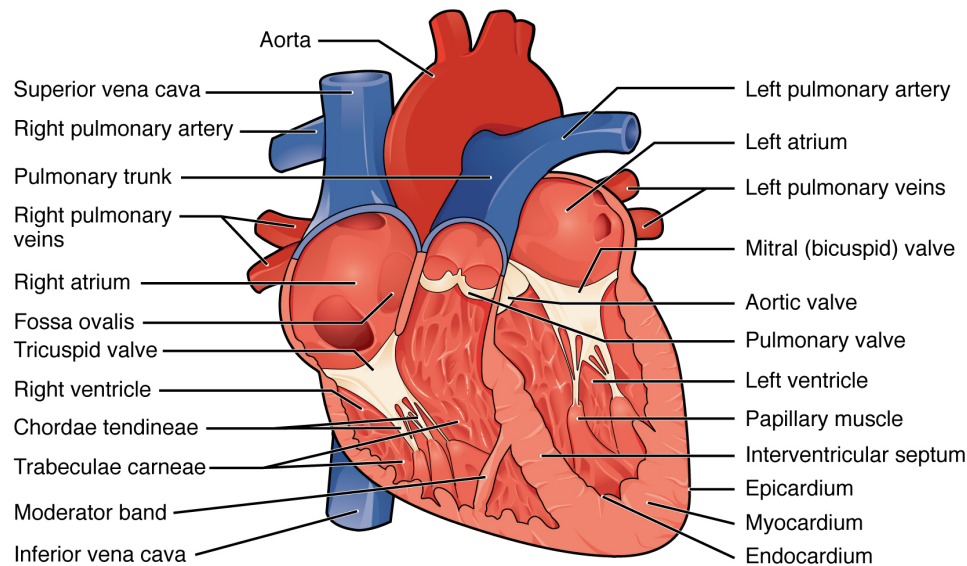
The word septum is derived from the Latin for “something that encloses;” in this case, a **septum** (plural = septa) refers to a wall or partition that divides the heart into chambers. The septa are physical extensions of the myocardium lined with endocardium. Located between the two atria is the **interatrial septum**. Normally in an adult heart, the interatrial septum bears an oval-shaped depression known as the **fossa ovalis**, a remnant of an opening in the fetal heart known as the **foramen ovale**. The foramen ovale allowed blood in the fetal heart to pass directly from the right atrium to the left atrium, allowing some blood to bypass the pulmonary circuit. Within seconds after birth, a flap of tissue known as the **septum primum** that previously acted as a valve closes the foramen ovale and establishes the typical cardiac circulation pattern.

Between the two ventricles is a second septum known as the **interventricular septum**. Unlike the interatrial septum, the interventricular

septum is normally intact after its formation during fetal development. It is substantially thicker than the interatrial septum, since the ventricles generate far greater pressure when they contract.

The septum between the atria and ventricles is known as the **atrioventricular septum**. It is marked by the presence of four openings that allow blood to move from the atria into the ventricles and from the ventricles into the pulmonary trunk and aorta. Located in each of these openings between the atria and ventricles is a **valve**, a specialized structure that ensures one-way flow of blood. The valves between the atria and ventricles are known generically as **atrioventricular valves**. The valves at the openings that lead to the pulmonary trunk and aorta are known generically as **semilunar valves**. The interventricular septum is visible in [\[link\]](#). In this figure, the atrioventricular septum has been removed to better show the bicupid and tricuspid valves; the interatrial septum is not visible, since its location is covered by the aorta and pulmonary trunk. Since these openings and valves structurally weaken the atrioventricular septum, the remaining tissue is heavily reinforced with dense connective tissue called the **cardiac skeleton**, or skeleton of the heart. It includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta, and serve as the point of attachment for the heart valves. The cardiac skeleton also provides an important boundary in the heart electrical conduction system.

Internal Structures of the Heart



Anterior view

This anterior view of the heart shows the four chambers, the major vessels and their early branches, as well as the valves. The presence of the pulmonary trunk and aorta covers the interatrial septum, and the atrioventricular septum is cut away to show the atrioventricular valves.

Note:

Disorders of the...

Heart: Heart Defects

One very common form of interatrial septum pathology is patent foramen ovale, which occurs when the septum primum does not close at birth, and the fossa ovalis is unable to fuse. The word patent is from the Latin root patens for “open.” It may be benign or asymptomatic, perhaps never being diagnosed, or in extreme cases, it may require surgical repair to close the opening permanently. As much as 20–25 percent of the general population may have a patent foramen ovale, but fortunately, most have the benign,

asymptomatic version. Patent foramen ovale is normally detected by auscultation of a heart murmur (an abnormal heart sound) and confirmed by imaging with an echocardiogram. Despite its prevalence in the general population, the causes of patent ovale are unknown, and there are no known risk factors. In nonlife-threatening cases, it is better to monitor the condition than to risk heart surgery to repair and seal the opening.

Coarctation of the aorta is a congenital abnormal narrowing of the aorta that is normally located at the insertion of the ligamentum arteriosum, the remnant of the fetal shunt called the ductus arteriosus. If severe, this condition drastically restricts blood flow through the primary systemic artery, which is life threatening. In some individuals, the condition may be fairly benign and not detected until later in life. Detectable symptoms in an infant include difficulty breathing, poor appetite, trouble feeding, or failure to thrive. In older individuals, symptoms include dizziness, fainting, shortness of breath, chest pain, fatigue, headache, and nosebleeds.

Treatment involves surgery to resect (remove) the affected region or angioplasty to open the abnormally narrow passageway. Studies have shown that the earlier the surgery is performed, the better the chance of survival.

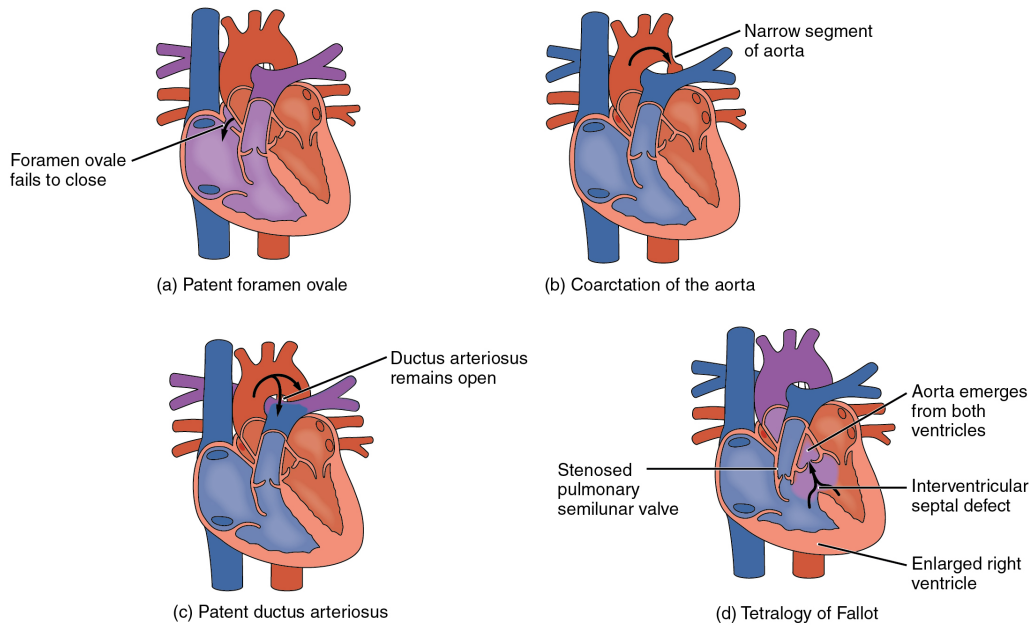
A patent ductus arteriosus is a congenital condition in which the ductus arteriosus fails to close. The condition may range from severe to benign. Failure of the ductus arteriosus to close results in blood flowing from the higher pressure aorta into the lower pressure pulmonary trunk. This additional fluid moving toward the lungs increases pulmonary pressure and makes respiration difficult. Symptoms include shortness of breath (dyspnea), tachycardia, enlarged heart, a widened pulse pressure, and poor weight gain in infants. Treatments include surgical closure (ligation), manual closure using platinum coils or specialized mesh inserted via the femoral artery or vein, or nonsteroidal anti-inflammatory drugs to block the synthesis of prostaglandin E₂, which maintains the vessel in an open position. If untreated, the condition can result in congestive heart failure. Septal defects are not uncommon in individuals and may be congenital or caused by various disease processes. Tetralogy of Fallot is a congenital condition that may also occur from exposure to unknown environmental factors; it occurs when there is an opening in the interventricular septum caused by blockage of the pulmonary trunk, normally at the pulmonary semilunar valve. This allows blood that is relatively low in oxygen from

the right ventricle to flow into the left ventricle and mix with the blood that is relatively high in oxygen. Symptoms include a distinct heart murmur, low blood oxygen percent saturation, dyspnea or difficulty in breathing, polycythemia, broadening (clubbing) of the fingers and toes, and in children, difficulty in feeding or failure to grow and develop. It is the most common cause of cyanosis following birth. The term “tetralogy” is derived from the four components of the condition, although only three may be present in an individual patient: pulmonary infundibular stenosis (rigidity of the pulmonary valve), overriding aorta (the aorta is shifted above both ventricles), ventricular septal defect (opening), and right ventricular hypertrophy (enlargement of the right ventricle). Other heart defects may also accompany this condition, which is typically confirmed by echocardiography imaging. Tetralogy of Fallot occurs in approximately 400 out of one million live births. Normal treatment involves extensive surgical repair, including the use of stents to redirect blood flow and replacement of valves and patches to repair the septal defect, but the condition has a relatively high mortality. Survival rates are currently 75 percent during the first year of life; 60 percent by 4 years of age; 30 percent by 10 years; and 5 percent by 40 years.

In the case of severe septal defects, including both tetralogy of Fallot and patent foramen ovale, failure of the heart to develop properly can lead to a condition commonly known as a “blue baby.” Regardless of normal skin pigmentation, individuals with this condition have an insufficient supply of oxygenated blood, which leads to cyanosis, a blue or purple coloration of the skin, especially when active.

Septal defects are commonly first detected through auscultation, listening to the chest using a stethoscope. In this case, instead of hearing normal heart sounds attributed to the flow of blood and closing of heart valves, unusual heart sounds may be detected. This is often followed by medical imaging to confirm or rule out a diagnosis. In many cases, treatment may not be needed. Some common congenital heart defects are illustrated in [\[link\]](#).

Congenital Heart Defects



(a) A patent foramen ovale defect is an abnormal opening in the interatrial septum, or more commonly, a failure of the foramen ovale to close. (b) Coarctation of the aorta is an abnormal narrowing of the aorta. (c) A patent ductus arteriosus is the failure of the ductus arteriosus to close. (d) Tetralogy of Fallot includes an abnormal opening in the interventricular septum.

Right Atrium

The right atrium serves as the receiving chamber for blood returning to the heart from the systemic circulation. The two major systemic veins, the superior and inferior venae cavae, and the large coronary vein called the **coronary sinus** that drains the heart myocardium empty into the right atrium. The superior vena cava drains blood from regions superior to the diaphragm: the head, neck, upper limbs, and the thoracic region. It empties into the superior and posterior portions of the right atrium. The inferior vena cava drains blood from areas inferior to the diaphragm: the lower limbs and abdominopelvic region of the body. It, too, empties into the

posterior portion of the atria, but inferior to the opening of the superior vena cava. Immediately superior and slightly medial to the opening of the inferior vena cava on the posterior surface of the atrium is the opening of the coronary sinus. This thin-walled vessel drains most of the coronary veins that return systemic blood from the heart. The majority of the internal heart structures discussed in this and subsequent sections are illustrated in [\[link\]](#).

While the bulk of the internal surface of the right atrium is smooth, the depression of the fossa ovalis is medial, and the anterior surface demonstrates prominent ridges of muscle called the **pectinate muscles**. The right auricle also has pectinate muscles. The left atrium does not have pectinate muscles except in the auricle.

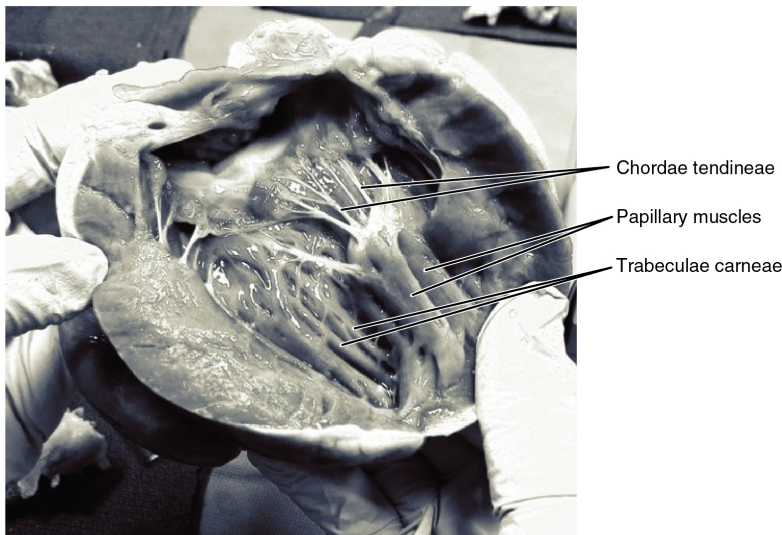
The atria receive venous blood on a nearly continuous basis, preventing venous flow from stopping while the ventricles are contracting. While most ventricular filling occurs while the atria are relaxed, they do demonstrate a contractile phase and actively pump blood into the ventricles just prior to ventricular contraction. The opening between the atrium and ventricle is guarded by the tricuspid valve.

Right Ventricle

The right ventricle receives blood from the right atrium through the tricuspid valve. Each flap of the valve is attached to strong strands of connective tissue, the **chordae tendineae**, literally “tendinous cords,” or sometimes more poetically referred to as “heart strings.” There are several chordae tendineae associated with each of the flaps. They are composed of approximately 80 percent collagenous fibers with the remainder consisting of elastic fibers and endothelium. They connect each of the flaps to a **papillary muscle** that extends from the inferior ventricular surface. There are three papillary muscles in the right ventricle, called the anterior, posterior, and septal muscles, which correspond to the three sections of the valves.

When the myocardium of the ventricle contracts, pressure within the ventricular chamber rises. Blood, like any fluid, flows from higher pressure to lower pressure areas, in this case, toward the pulmonary trunk and the atrium. To prevent any potential backflow, the papillary muscles also contract, generating tension on the chordae tendineae. This prevents the flaps of the valves from being forced into the atria and regurgitation of the blood back into the atria during ventricular contraction. [\[link\]](#) shows papillary muscles and chordae tendineae attached to the tricuspid valve.

Chordae Tendineae and Papillary Muscles



In this frontal section, you can see papillary muscles attached to the tricuspid valve on the right as well as the mitral valve on the left via chordae tendineae. (credit: modification of work by “PV KS”/flickr.com)

The walls of the ventricle are lined with **trabeculae carneae**, ridges of cardiac muscle covered by endocardium. In addition to these muscular ridges, a band of cardiac muscle, also covered by endocardium, known as the **moderator band** (see [\[link\]](#)) reinforces the thin walls of the right ventricle and plays a crucial role in cardiac conduction. It arises from the

inferior portion of the interventricular septum and crosses the interior space of the right ventricle to connect with the inferior papillary muscle.

When the right ventricle contracts, it ejects blood into the pulmonary trunk, which branches into the left and right pulmonary arteries that carry it to each lung. The superior surface of the right ventricle begins to taper as it approaches the pulmonary trunk. At the base of the pulmonary trunk is the pulmonary semilunar valve that prevents backflow from the pulmonary trunk.

Left Atrium

After exchange of gases in the pulmonary capillaries, blood returns to the left atrium high in oxygen via one of the four pulmonary veins. While the left atrium does not contain pectinate muscles, it does have an auricle that includes these pectinate ridges. Blood flows nearly continuously from the pulmonary veins back into the atrium, which acts as the receiving chamber, and from here through an opening into the left ventricle. Most blood flows passively into the heart while both the atria and ventricles are relaxed, but toward the end of the ventricular relaxation period, the left atrium will contract, pumping blood into the ventricle. This atrial contraction accounts for approximately 20 percent of ventricular filling. The opening between the left atrium and ventricle is guarded by the mitral valve.

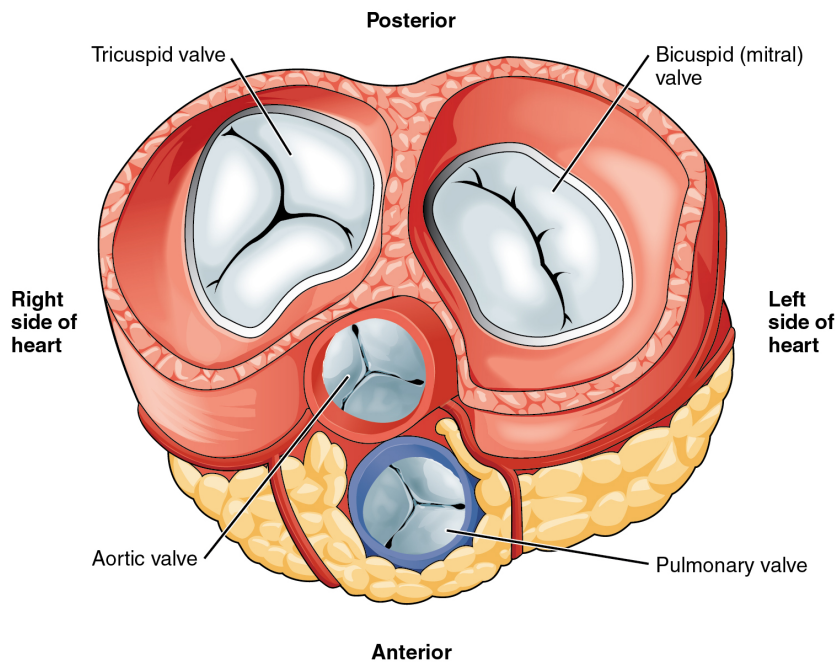
Left Ventricle

Recall that, although both sides of the heart will pump the same amount of blood, the muscular layer is much thicker in the left ventricle compared to the right (see [\[link\]](#)). Like the right ventricle, the left also has trabeculae carneae, but there is no moderator band. The mitral valve is connected to papillary muscles via chordae tendineae. There are two papillary muscles on the left—the anterior and posterior—as opposed to three on the right.

The left ventricle is the major pumping chamber for the systemic circuit; it ejects blood into the aorta through the aortic semilunar valve.

Heart Valve Structure and Function

A transverse section through the heart slightly above the level of the atrioventricular septum reveals all four heart valves along the same plane ([link](#)). The valves ensure unidirectional blood flow through the heart. Between the right atrium and the right ventricle is the **right atrioventricular valve**, or **tricuspid valve**. It typically consists of three flaps, or leaflets, made of endocardium reinforced with additional connective tissue. The flaps are connected by chordae tendineae to the papillary muscles, which control the opening and closing of the valves. Heart Valves



With the atria and major vessels removed, all four valves are clearly visible, although it is difficult to distinguish the three separate cusps of the tricuspid valve.

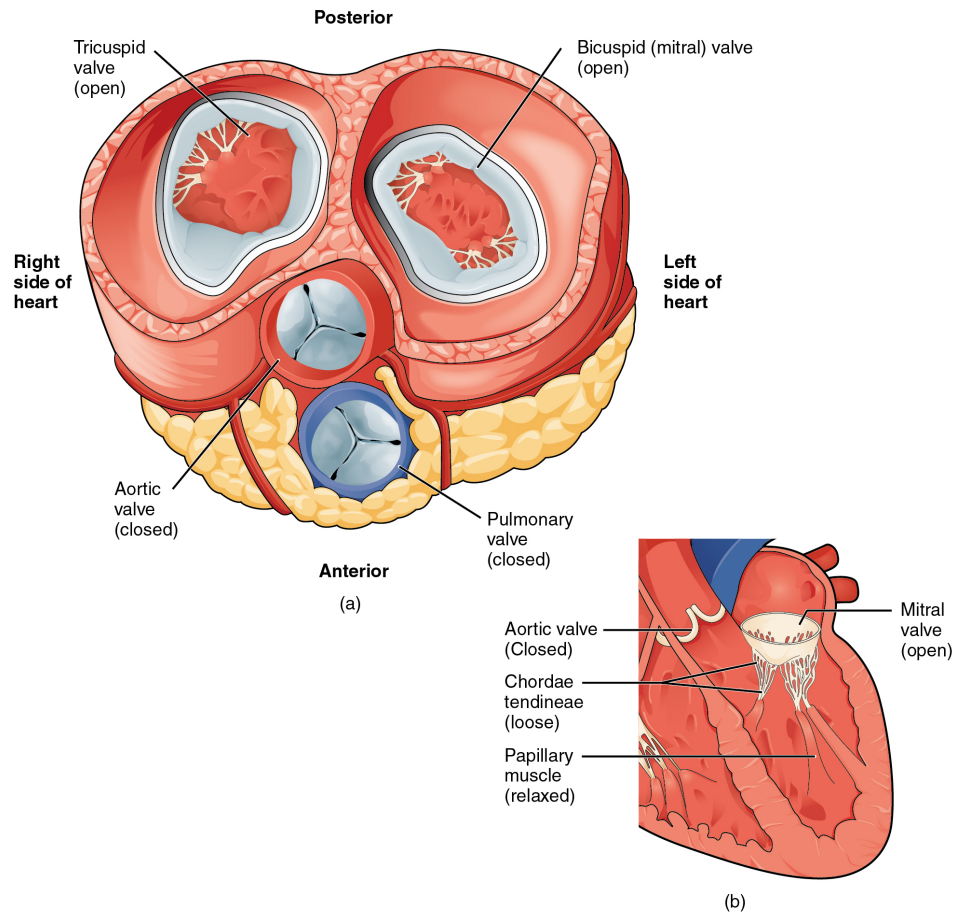
Emerging from the right ventricle at the base of the pulmonary trunk is the pulmonary semilunar valve, or the **pulmonary valve**; it is also known as the pulmonic valve or the right semilunar valve. The pulmonary valve is comprised of three small flaps of endothelium reinforced with connective tissue. When the ventricle relaxes, the pressure differential causes blood to flow back into the ventricle from the pulmonary trunk. This flow of blood fills the pocket-like flaps of the pulmonary valve, causing the valve to close and producing an audible sound. Unlike the atrioventricular valves, there are no papillary muscles or chordae tendineae associated with the pulmonary valve.

Located at the opening between the left atrium and left ventricle is the **mitral valve**, also called the **bicuspid valve** or the **left atrioventricular valve**. Structurally, this valve consists of two cusps, known as the anterior medial cusp and the posterior medial cusp, compared to the three cusps of the tricuspid valve. In a clinical setting, the valve is referred to as the mitral valve, rather than the bicuspid valve. The two cusps of the mitral valve are attached by chordae tendineae to two papillary muscles that project from the wall of the ventricle.

At the base of the aorta is the aortic semilunar valve, or the **aortic valve**, which prevents backflow from the aorta. It normally is composed of three flaps. When the ventricle relaxes and blood attempts to flow back into the ventricle from the aorta, blood will fill the cusps of the valve, causing it to close and producing an audible sound.

In [\[link\]](#)**a**, the two atrioventricular valves are open and the two semilunar valves are closed. This occurs when both atria and ventricles are relaxed and when the atria contract to pump blood into the ventricles. [\[link\]](#)**b** shows a frontal view. Although only the left side of the heart is illustrated, the process is virtually identical on the right.

Blood Flow from the Left Atrium to the Left Ventricle

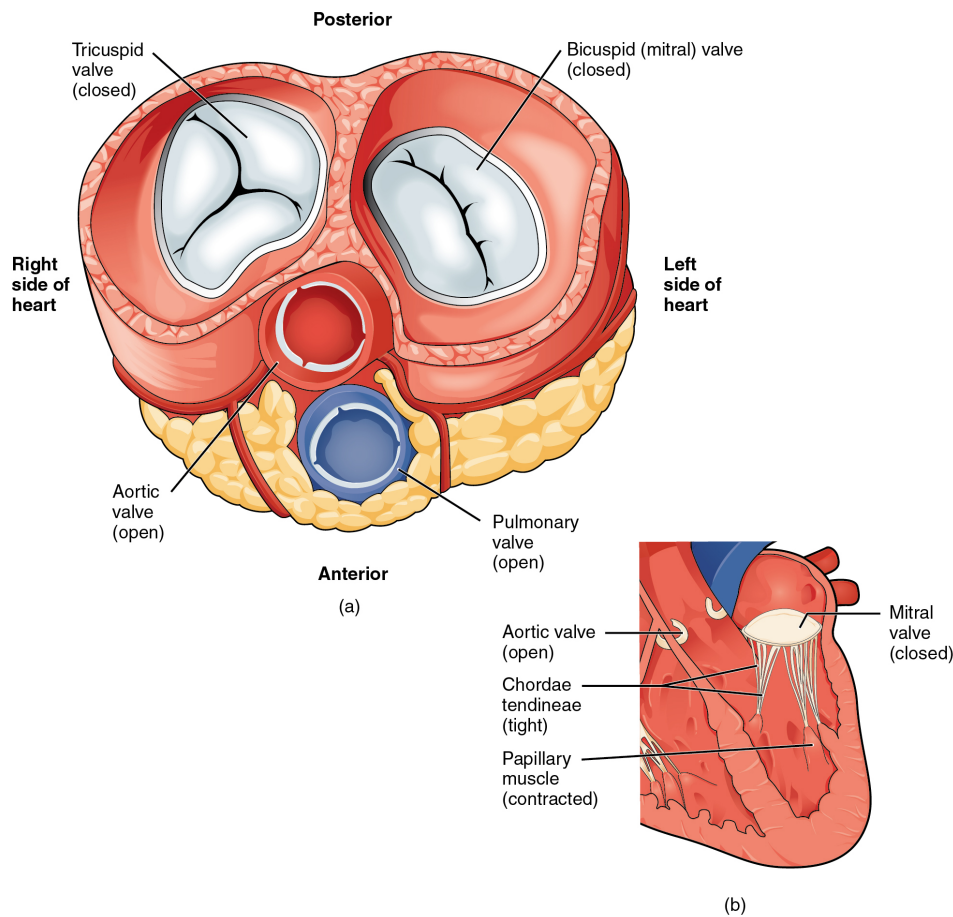


(a) A transverse section through the heart illustrates the four heart valves. The two atrioventricular valves are open; the two semilunar valves are closed. The atria and vessels have been removed. (b) A frontal section through the heart illustrates blood flow through the mitral valve. When the mitral valve is open, it allows blood to move from the left atrium to the left ventricle. The aortic semilunar valve is closed to prevent backflow of blood from the aorta to the left ventricle.

[\[link\]](#) a shows the atrioventricular valves closed while the two semilunar valves are open. This occurs when the ventricles contract to eject blood into the pulmonary trunk and aorta. Closure of the two atrioventricular valves

prevents blood from being forced back into the atria. This stage can be seen from a frontal view in [\[link\]](#)**b**.

Blood Flow from the Left Ventricle into the Great Vessels



(a) A transverse section through the heart illustrates the four heart valves during ventricular contraction. The two atrioventricular valves are closed, but the two semilunar valves are open. The atria and vessels have been removed. (b) A frontal view shows the closed mitral (bicuspid) valve that prevents backflow of blood into the left atrium. The aortic semilunar valve is open to allow blood to be ejected into the aorta.

When the ventricles begin to contract, pressure within the ventricles rises and blood flows toward the area of lowest pressure, which is initially in the

atria. This backflow causes the cusps of the tricuspid and mitral (bicuspid) valves to close. These valves are tied down to the papillary muscles by chordae tendineae. During the relaxation phase of the cardiac cycle, the papillary muscles are also relaxed and the tension on the chordae tendineae is slight (see [\[link\]](#)**b**). However, as the myocardium of the ventricle contracts, so do the papillary muscles. This creates tension on the chordae tendineae (see [\[link\]](#)**b**), helping to hold the cusps of the atrioventricular valves in place and preventing them from being blown back into the atria.

The aortic and pulmonary semilunar valves lack the chordae tendineae and papillary muscles associated with the atrioventricular valves. Instead, they consist of pocket-like folds of endocardium reinforced with additional connective tissue. When the ventricles relax and the change in pressure forces the blood toward the ventricles, the blood presses against these cusps and seals the openings.

Note:



Visit this [site](#) to observe an echocardiogram of actual heart valves opening and closing. Although much of the heart has been “removed” from this gif loop so the chordae tendineae are not visible, why is their presence more critical for the atrioventricular valves (tricuspid and mitral) than the semilunar (aortic and pulmonary) valves?

Note:

Disorders of the...
Heart Valves

When heart valves do not function properly, they are often described as incompetent and result in valvular heart disease, which can range from benign to lethal. Some of these conditions are congenital, that is, the individual was born with the defect, whereas others may be attributed to disease processes or trauma. Some malfunctions are treated with medications, others require surgery, and still others may be mild enough that the condition is merely monitored since treatment might trigger more serious consequences.

Valvular disorders are often caused by carditis, or inflammation of the heart. One common trigger for this inflammation is rheumatic fever, or scarlet fever, an autoimmune response to the presence of a bacterium, *Streptococcus pyogenes*, normally a disease of childhood.

While any of the heart valves may be involved in valve disorders, mitral regurgitation is the most common, detected in approximately 2 percent of the population, and the pulmonary semilunar valve is the least frequently involved. When a valve malfunctions, the flow of blood to a region will often be disrupted. The resulting inadequate flow of blood to this region will be described in general terms as an insufficiency. The specific type of insufficiency is named for the valve involved: aortic insufficiency, mitral insufficiency, tricuspid insufficiency, or pulmonary insufficiency.

If one of the cusps of the valve is forced backward by the force of the blood, the condition is referred to as a prolapsed valve. Prolapse may occur if the chordae tendineae are damaged or broken, causing the closure mechanism to fail. The failure of the valve to close properly disrupts the normal one-way flow of blood and results in regurgitation, when the blood flows backward from its normal path. Using a stethoscope, the disruption to the normal flow of blood produces a heart murmur.

Stenosis is a condition in which the heart valves become rigid and may calcify over time. The loss of flexibility of the valve interferes with normal function and may cause the heart to work harder to propel blood through the valve, which eventually weakens the heart. Aortic stenosis affects approximately 2 percent of the population over 65 years of age, and the percentage increases to approximately 4 percent in individuals over 85 years. Occasionally, one or more of the chordae tendineae will tear or the papillary muscle itself may die as a component of a myocardial infarction (heart attack). In this case, the patient's condition will deteriorate

dramatically and rapidly, and immediate surgical intervention may be required.

Auscultation, or listening to a patient's heart sounds, is one of the most useful diagnostic tools, since it is proven, safe, and inexpensive. The term auscultation is derived from the Latin for "to listen," and the technique has been used for diagnostic purposes as far back as the ancient Egyptians. Valve and septal disorders will trigger abnormal heart sounds. If a valvular disorder is detected or suspected, a test called an echocardiogram, or simply an "echo," may be ordered. Echocardiograms are sonograms of the heart and can help in the diagnosis of valve disorders as well as a wide variety of heart pathologies.

Note:



Visit this [site](#) for a free download, including excellent animations and audio of heart sounds.

Note:

Career Connection

Cardiologist

Cardiologists are medical doctors that specialize in the diagnosis and treatment of diseases of the heart. After completing 4 years of medical school, cardiologists complete a three-year residency in internal medicine followed by an additional three or more years in cardiology. Following this 10-year period of medical training and clinical experience, they qualify for a rigorous two-day examination administered by the Board of Internal Medicine that tests their academic training and clinical abilities, including

diagnostics and treatment. After successful completion of this examination, a physician becomes a board-certified cardiologist. Some board-certified cardiologists may be invited to become a Fellow of the American College of Cardiology (FACC). This professional recognition is awarded to outstanding physicians based upon merit, including outstanding credentials, achievements, and community contributions to cardiovascular medicine.

Note:



Visit this [site](#) to learn more about cardiologists.

Note:

Career Connection

Cardiovascular Technologist/Technician

Cardiovascular technologists/technicians are trained professionals who perform a variety of imaging techniques, such as sonograms or echocardiograms, used by physicians to diagnose and treat diseases of the heart. Nearly all of these positions require an associate degree, and these technicians earn a median salary of \$49,410 as of May 2010, according to the U.S. Bureau of Labor Statistics. Growth within the field is fast, projected at 29 percent from 2010 to 2020.

There is a considerable overlap and complementary skills between cardiac technicians and vascular technicians, and so the term cardiovascular technician is often used. Special certifications within the field require documenting appropriate experience and completing additional and often expensive certification examinations. These subspecialties include

Certified Rhythm Analysis Technician (CRAT), Certified Cardiographic Technician (CCT), Registered Congenital Cardiac Sonographer (RCCS), Registered Cardiac Electrophysiology Specialist (RCES), Registered Cardiovascular Invasive Specialist (RCIS), Registered Cardiac Sonographer (RCS), Registered Vascular Specialist (RVS), and Registered Phlebology Sonographer (RPhS).

Note:



Visit this [site](#) for more information on cardiovascular technologists/technicians.

Coronary Circulation

You will recall that the heart is a remarkable pump composed largely of cardiac muscle cells that are incredibly active throughout life. Like all other cells, a **cardiomyocyte** requires a reliable supply of oxygen and nutrients, and a way to remove wastes, so it needs a dedicated, complex, and extensive coronary circulation. And because of the critical and nearly ceaseless activity of the heart throughout life, this need for a blood supply is even greater than for a typical cell. However, coronary circulation is not continuous; rather, it cycles, reaching a peak when the heart muscle is relaxed and nearly ceasing while it is contracting.

Coronary Arteries

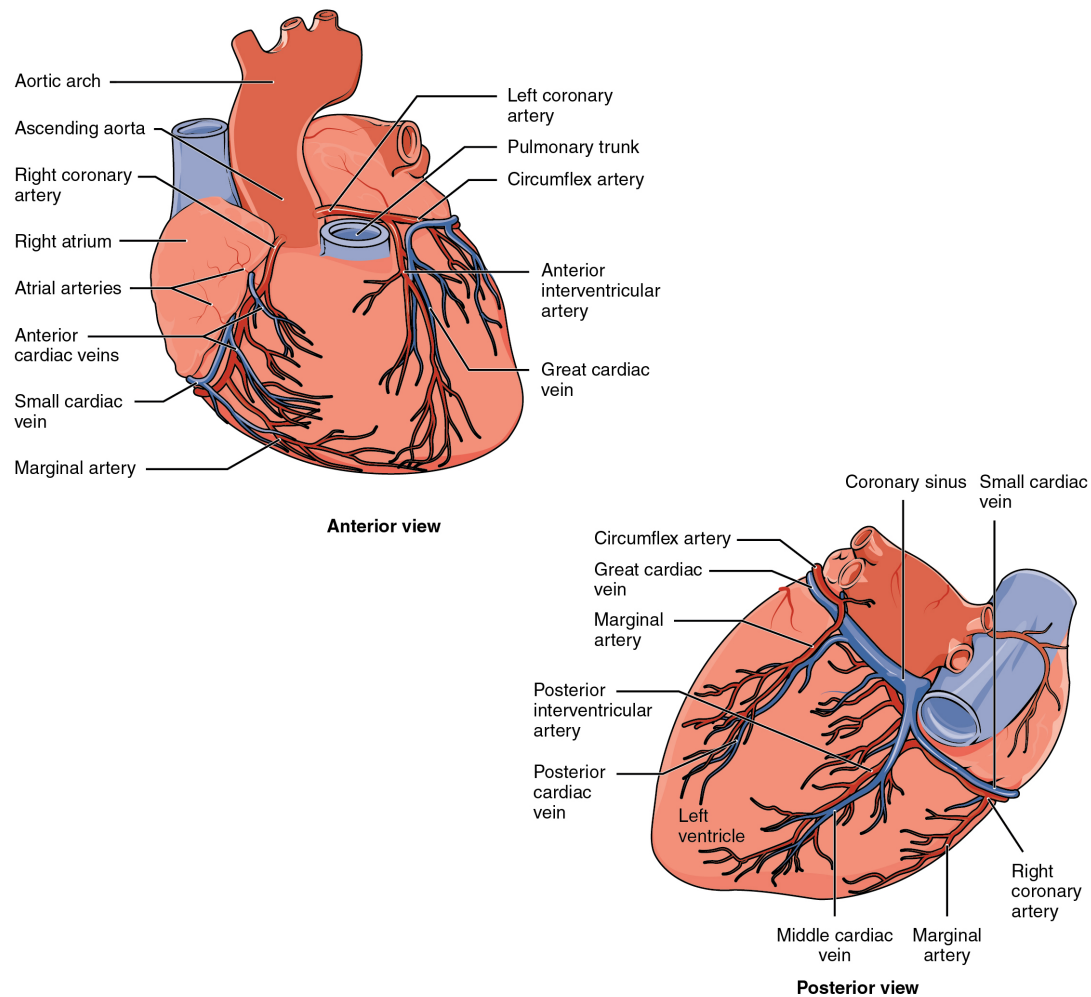
Coronary arteries supply blood to the myocardium and other components of the heart. The first portion of the aorta after it arises from the left ventricle gives rise to the coronary arteries. There are three dilations in the wall of the aorta just superior to the aortic semilunar valve. Two of these, the left posterior aortic sinus and anterior aortic sinus, give rise to the left and right coronary arteries, respectively. The third sinus, the right posterior aortic sinus, typically does not give rise to a vessel. Coronary vessel branches that remain on the surface of the artery and follow the sulci are called **epicardial coronary arteries**.

The left coronary artery distributes blood to the left side of the heart, the left atrium and ventricle, and the interventricular septum. The **circumflex artery** arises from the left coronary artery and follows the coronary sulcus to the left. Eventually, it will fuse with the small branches of the right coronary artery. The larger **anterior interventricular artery**, also known as the left anterior descending artery (LAD), is the second major branch arising from the left coronary artery. It follows the anterior interventricular sulcus around the pulmonary trunk. Along the way it gives rise to numerous smaller branches that interconnect with the branches of the posterior interventricular artery, forming anastomoses. An **anastomosis** is an area where vessels unite to form interconnections that normally allow blood to circulate to a region even if there may be partial blockage in another branch. The anastomoses in the heart are very small. Therefore, this ability is somewhat restricted in the heart so a coronary artery blockage often results in death of the cells (myocardial infarction) supplied by the particular vessel.

The right coronary artery proceeds along the coronary sulcus and distributes blood to the right atrium, portions of both ventricles, and the heart conduction system. Normally, one or more marginal arteries arise from the right coronary artery inferior to the right atrium. The **marginal arteries** supply blood to the superficial portions of the right ventricle. On the posterior surface of the heart, the right coronary artery gives rise to the **posterior interventricular artery**, also known as the posterior descending artery. It runs along the posterior portion of the interventricular sulcus toward the apex of the heart, giving rise to branches that supply the interventricular septum and portions of both ventricles. [\[link\]](#) presents

views of the coronary circulation from both the anterior and posterior views.

Coronary Circulation



The anterior view of the heart shows the prominent coronary surface vessels. The posterior view of the heart shows the prominent coronary surface vessels.

Note:

Diseases of the...

Heart: Myocardial Infarction

Myocardial infarction (MI) is the formal term for what is commonly referred to as a heart attack. It normally results from a lack of blood flow (ischemia) and oxygen (hypoxia) to a region of the heart, resulting in death of the cardiac muscle cells. An MI often occurs when a coronary artery is blocked by the buildup of atherosclerotic plaque consisting of lipids, cholesterol and fatty acids, and white blood cells, primarily macrophages. It can also occur when a portion of an unstable atherosclerotic plaque travels through the coronary arterial system and lodges in one of the smaller vessels. The resulting blockage restricts the flow of blood and oxygen to the myocardium and causes death of the tissue. MIs may be triggered by excessive exercise, in which the partially occluded artery is no longer able to pump sufficient quantities of blood, or severe stress, which may induce spasm of the smooth muscle in the walls of the vessel.

In the case of acute MI, there is often sudden pain beneath the sternum (retrosternal pain) called angina pectoris, often radiating down the left arm in males but not in female patients. Until this anomaly between the sexes was discovered, many female patients suffering MIs were misdiagnosed and sent home. In addition, patients typically present with difficulty breathing and shortness of breath (dyspnea), irregular heartbeat (palpations), nausea and vomiting, sweating (diaphoresis), anxiety, and fainting (syncope), although not all of these symptoms may be present. Many of the symptoms are shared with other medical conditions, including anxiety attacks and simple indigestion, so differential diagnosis is critical. It is estimated that between 22 and 64 percent of MIs present without any symptoms.

An MI can be confirmed by examining the patient's ECG, which frequently reveals alterations in the ST and Q components. Some classification schemes of MI are referred to as ST-elevated MI (STEMI) and non-elevated MI (non-STEMI). In addition, echocardiography or cardiac magnetic resonance imaging may be employed. Common blood tests indicating an MI include elevated levels of creatine kinase MB (an enzyme that catalyzes the conversion of creatine to phosphocreatine, consuming ATP) and cardiac troponin (the regulatory protein for muscle contraction), both of which are released by damaged cardiac muscle cells. Immediate treatments for MI are essential and include administering supplemental oxygen, aspirin that helps to break up clots, and nitroglycerine administered sublingually (under the tongue) to facilitate its

absorption. Despite its unquestioned success in treatments and use since the 1880s, the mechanism of nitroglycerine is still incompletely understood but is believed to involve the release of nitric oxide, a known vasodilator, and endothelium-derived releasing factor, which also relaxes the smooth muscle in the tunica media of coronary vessels. Longer-term treatments include injections of thrombolytic agents such as streptokinase that dissolve the clot, the anticoagulant heparin, balloon angioplasty and stents to open blocked vessels, and bypass surgery to allow blood to pass around the site of blockage. If the damage is extensive, coronary replacement with a donor heart or coronary assist device, a sophisticated mechanical device that supplements the pumping activity of the heart, may be employed. Despite the attention, development of artificial hearts to augment the severely limited supply of heart donors has proven less than satisfactory but will likely improve in the future.

MIIs may trigger cardiac arrest, but the two are not synonymous. Important risk factors for MI include cardiovascular disease, age, smoking, high blood levels of the low-density lipoprotein (LDL, often referred to as “bad” cholesterol), low levels of high-density lipoprotein (HDL, or “good” cholesterol), hypertension, diabetes mellitus, obesity, lack of physical exercise, chronic kidney disease, excessive alcohol consumption, and use of illegal drugs.

Coronary Veins

Coronary veins drain the heart and generally parallel the large surface arteries (see [\[link\]](#)). The **great cardiac vein** can be seen initially on the surface of the heart following the interventricular sulcus, but it eventually flows along the coronary sulcus into the coronary sinus on the posterior surface. The great cardiac vein initially parallels the anterior interventricular artery and drains the areas supplied by this vessel. It receives several major branches, including the posterior cardiac vein, the middle cardiac vein, and the small cardiac vein. The **posterior cardiac vein** parallels and drains the areas supplied by the marginal artery branch of the circumflex artery. The **middle cardiac vein** parallels and drains the areas supplied by the posterior interventricular artery. The **small cardiac vein**

parallels the right coronary artery and drains the blood from the posterior surfaces of the right atrium and ventricle. The coronary sinus is a large, thin-walled vein on the posterior surface of the heart lying within the atrioventricular sulcus and emptying directly into the right atrium. The **anterior cardiac veins** parallel the small cardiac arteries and drain the anterior surface of the right ventricle. Unlike these other cardiac veins, it bypasses the coronary sinus and drains directly into the right atrium.

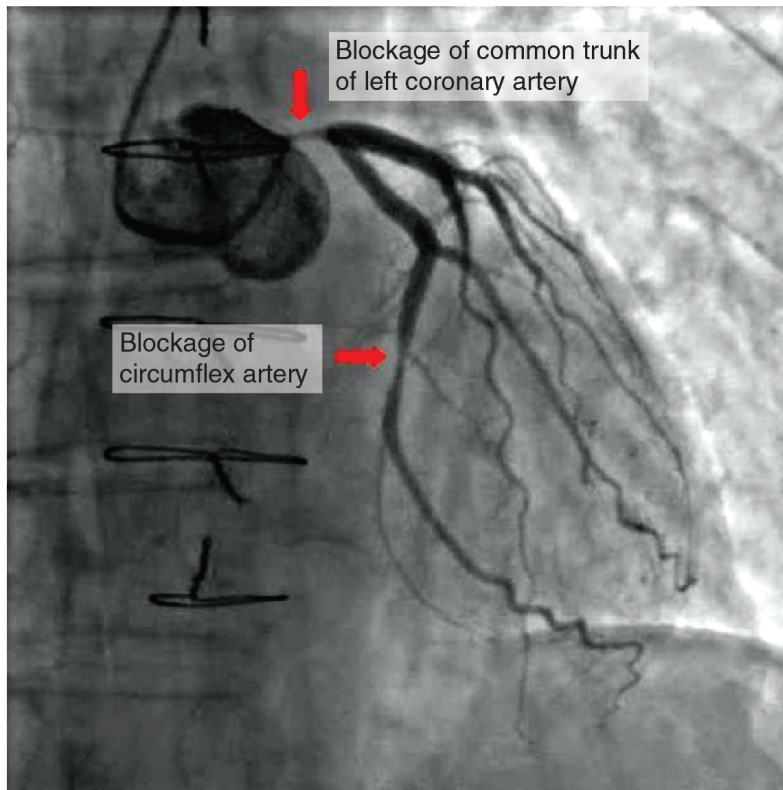
Note:

Diseases of the...

Heart: Coronary Artery Disease

Coronary artery disease is the leading cause of death worldwide. It occurs when the buildup of plaque—a fatty material including cholesterol, connective tissue, white blood cells, and some smooth muscle cells—within the walls of the arteries obstructs the flow of blood and decreases the flexibility or compliance of the vessels. This condition is called atherosclerosis, a hardening of the arteries that involves the accumulation of plaque. As the coronary blood vessels become occluded, the flow of blood to the tissues will be restricted, a condition called ischemia that causes the cells to receive insufficient amounts of oxygen, called hypoxia. [\[link\]](#) shows the blockage of coronary arteries highlighted by the injection of dye. Some individuals with coronary artery disease report pain radiating from the chest called angina pectoris, but others remain asymptomatic. If untreated, coronary artery disease can lead to MI or a heart attack.

Atherosclerotic Coronary Arteries



In this coronary angiogram (X-ray), the dye makes visible two occluded coronary arteries. Such blockages can lead to decreased blood flow (ischemia) and insufficient oxygen (hypoxia) delivered to the cardiac tissues. If uncorrected, this can lead to cardiac muscle death (myocardial infarction).

The disease progresses slowly and often begins in children and can be seen as fatty “streaks” in the vessels. It then gradually progresses throughout life. Well-documented risk factors include smoking, family history, hypertension, obesity, diabetes, high alcohol consumption, lack of exercise, stress, and hyperlipidemia or high circulating levels of lipids in the blood. Treatments may include medication, changes to diet and exercise, angioplasty with a balloon catheter, insertion of a stent, or coronary bypass procedure.

Angioplasty is a procedure in which the occlusion is mechanically widened with a balloon. A specialized catheter with an expandable tip is inserted into a superficial vessel, normally in the leg, and then directed to the site of the occlusion. At this point, the balloon is inflated to compress the plaque material and to open the vessel to increase blood flow. Then, the balloon is deflated and retracted. A stent consisting of a specialized mesh is typically inserted at the site of occlusion to reinforce the weakened and damaged walls. Stent insertions have been routine in cardiology for more than 40 years.

Coronary bypass surgery may also be performed. This surgical procedure grafts a replacement vessel obtained from another, less vital portion of the body to bypass the occluded area. This procedure is clearly effective in treating patients experiencing a MI, but overall does not increase longevity. Nor does it seem advisable in patients with stable although diminished cardiac capacity since frequently loss of mental acuity occurs following the procedure. Long-term changes to behavior, emphasizing diet and exercise plus a medicine regime tailored to lower blood pressure, lower cholesterol and lipids, and reduce clotting are equally as effective.

Chapter Review

The heart resides within the pericardial sac and is located in the mediastinal space within the thoracic cavity. The pericardial sac consists of two fused layers: an outer fibrous capsule and an inner parietal pericardium lined with a serous membrane. Between the pericardial sac and the heart is the pericardial cavity, which is filled with lubricating serous fluid. The walls of the heart are composed of an outer epicardium, a thick myocardium, and an inner lining layer of endocardium. The human heart consists of a pair of atria, which receive blood and pump it into a pair of ventricles, which pump blood into the vessels. The right atrium receives systemic blood relatively low in oxygen and pumps it into the right ventricle, which pumps it into the pulmonary circuit. Exchange of oxygen and carbon dioxide occurs in the lungs, and blood high in oxygen returns to the left atrium, which pumps blood into the left ventricle, which in turn pumps blood into the aorta and the remainder of the systemic circuit. The septa are the partitions that

separate the chambers of the heart. They include the interatrial septum, the interventricular septum, and the atrioventricular septum. Two of these openings are guarded by the atrioventricular valves, the right tricuspid valve and the left mitral valve, which prevent the backflow of blood. Each is attached to chordae tendineae that extend to the papillary muscles, which are extensions of the myocardium, to prevent the valves from being blown back into the atria. The pulmonary valve is located at the base of the pulmonary trunk, and the left semilunar valve is located at the base of the aorta. The right and left coronary arteries are the first to branch off the aorta and arise from two of the three sinuses located near the base of the aorta and are generally located in the sulci. Cardiac veins parallel the small cardiac arteries and generally drain into the coronary sinus.

Interactive Link Questions

Exercise:

Problem:

Visit this [site](#) to observe an echocardiogram of actual heart valves opening and closing. Although much of the heart has been “removed” from this gif loop so the chordae tendineae are not visible, why is their presence more critical for the atrioventricular valves (tricuspid and mitral) than the semilunar (aortic and pulmonary) valves?

Solution:

The pressure gradient between the atria and the ventricles is much greater than that between the ventricles and the pulmonary trunk and aorta. Without the presence of the chordae tendineae and papillary muscles, the valves would be blown back (prolapsed) into the atria and blood would regurgitate.

Review Questions

Exercise:

Problem:

Which of the following is not important in preventing backflow of blood?

- a. chordae tendineae
- b. papillary muscles
- c. AV valves
- d. endocardium

Solution:

D

Exercise:

Problem: Which valve separates the left atrium from the left ventricle?

- a. mitral
- b. tricuspid
- c. pulmonary
- d. aortic

Solution:

A

Exercise:**Problem:**

Which of the following lists the valves in the order through which the blood flows from the vena cava through the heart?

- a. tricuspid, pulmonary semilunar, bicuspid, aortic semilunar
- b. mitral, pulmonary semilunar, bicuspid, aortic semilunar
- c. aortic semilunar, pulmonary semilunar, tricuspid, bicuspid

d. bicuspid, aortic semilunar, tricuspid, pulmonary semilunar

Solution:

A

Exercise:

Problem:

Which chamber initially receives blood from the systemic circuit?

- a. left atrium
 - b. left ventricle
 - c. right atrium
 - d. right ventricle
-

Solution:

C

Exercise:

Problem:

The _____ layer secretes chemicals that help to regulate ionic environments and strength of contraction and serve as powerful vasoconstrictors.

- a. pericardial sac
 - b. endocardium
 - c. myocardium
 - d. epicardium
-

Solution:

B

Exercise:

Problem: The myocardium would be the thickest in the _____.

- a. left atrium
- b. left ventricle
- c. right atrium
- d. right ventricle

Solution:

B

Exercise:

Problem: In which septum is it normal to find openings in the adult?

- a. interatrial septum
- b. interventricular septum
- c. atrioventricular septum
- d. all of the above

Solution:

C

Critical Thinking Questions**Exercise:****Problem:**

Describe how the valves keep the blood moving in one direction.

Solution:

When the ventricles contract and pressure begins to rise in the ventricles, there is an initial tendency for blood to flow back (regurgitate) to the atria. However, the papillary muscles also contract, placing tension on the chordae tendineae and holding the atrioventricular valves (tricuspid and mitral) in place to prevent the valves from prolapsing and being forced back into the atria. The semilunar valves (pulmonary and aortic) lack chordae tendineae and papillary muscles, but do not face the same pressure gradients as do the atrioventricular valves. As the ventricles relax and pressure drops within the ventricles, there is a tendency for the blood to flow backward. However, the valves, consisting of reinforced endothelium and connective tissue, fill with blood and seal off the opening preventing the return of blood.

Exercise:**Problem:**

Why is the pressure in the pulmonary circulation lower than in the systemic circulation?

Solution:

The pulmonary circuit consists of blood flowing to and from the lungs, whereas the systemic circuit carries blood to and from the entire body. The systemic circuit is far more extensive, consisting of far more vessels and offers much greater resistance to the flow of blood, so the heart must generate a higher pressure to overcome this resistance. This can be seen in the thickness of the myocardium in the ventricles.

Glossary

anastomosis

(plural = anastomoses) area where vessels unite to allow blood to circulate even if there may be partial blockage in another branch

anterior cardiac veins

vessels that parallel the small cardiac arteries and drain the anterior surface of the right ventricle; bypass the coronary sinus and drain directly into the right atrium

anterior interventricular artery

(also, left anterior descending artery or LAD) major branch of the left coronary artery that follows the anterior interventricular sulcus

anterior interventricular sulcus

sulcus located between the left and right ventricles on the anterior surface of the heart

aortic valve

(also, aortic semilunar valve) valve located at the base of the aorta

atrioventricular septum

cardiac septum located between the atria and ventricles; atrioventricular valves are located here

atrioventricular valves

one-way valves located between the atria and ventricles; the valve on the right is called the tricuspid valve, and the one on the left is the mitral or bicuspid valve

atrium

(plural = atria) upper or receiving chamber of the heart that pumps blood into the lower chambers just prior to their contraction; the right atrium receives blood from the systemic circuit that flows into the right ventricle; the left atrium receives blood from the pulmonary circuit that flows into the left ventricle

auricle

extension of an atrium visible on the superior surface of the heart

bicuspid valve

(also, mitral valve or left atrioventricular valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

cardiac notch

depression in the medial surface of the inferior lobe of the left lung where the apex of the heart is located

cardiac skeleton

(also, skeleton of the heart) reinforced connective tissue located within the atrioventricular septum; includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta; the point of attachment for the heart valves

cardiomyocyte

muscle cell of the heart

chordae tendineae

string-like extensions of tough connective tissue that extend from the flaps of the atrioventricular valves to the papillary muscles

circumflex artery

branch of the left coronary artery that follows coronary sulcus

coronary arteries

branches of the ascending aorta that supply blood to the heart; the left coronary artery feeds the left side of the heart, the left atrium and ventricle, and the interventricular septum; the right coronary artery feeds the right atrium, portions of both ventricles, and the heart conduction system

coronary sinus

large, thin-walled vein on the posterior surface of the heart that lies within the atrioventricular sulcus and drains the heart myocardium directly into the right atrium

coronary sulcus

sulcus that marks the boundary between the atria and ventricles

coronary veins

vessels that drain the heart and generally parallel the large surface arteries

endocardium

innermost layer of the heart lining the heart chambers and heart valves;
composed of endothelium reinforced with a thin layer of connective
tissue that binds to the myocardium

endothelium

layer of smooth, simple squamous epithelium that lines the
endocardium and blood vessels

epicardial coronary arteries

surface arteries of the heart that generally follow the sulci

epicardium

innermost layer of the serous pericardium and the outermost layer of
the heart wall

foramen ovale

opening in the fetal heart that allows blood to flow directly from the
right atrium to the left atrium, bypassing the fetal pulmonary circuit

fossa ovalis

oval-shaped depression in the interatrial septum that marks the former
location of the foramen ovale

great cardiac vein

vessel that follows the interventricular sulcus on the anterior surface of
the heart and flows along the coronary sulcus into the coronary sinus
on the posterior surface; parallels the anterior interventricular artery
and drains the areas supplied by this vessel

hypertrophic cardiomyopathy

pathological enlargement of the heart, generally for no known reason

inferior vena cava

large systemic vein that returns blood to the heart from the inferior
portion of the body

interatrial septum

cardiac septum located between the two atria; contains the fossa ovalis after birth

interventricular septum

cardiac septum located between the two ventricles

left atrioventricular valve

(also, mitral valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

marginal arteries

branches of the right coronary artery that supply blood to the superficial portions of the right ventricle

mesothelium

simple squamous epithelial portion of serous membranes, such as the superficial portion of the epicardium (the visceral pericardium) and the deepest portion of the pericardium (the parietal pericardium)

middle cardiac vein

vessel that parallels and drains the areas supplied by the posterior interventricular artery; drains into the great cardiac vein

mitral valve

(also, left atrioventricular valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

moderator band

band of myocardium covered by endocardium that arises from the inferior portion of the interventricular septum in the right ventricle and crosses to the anterior papillary muscle; contains conductile fibers that carry electrical signals followed by contraction of the heart

myocardium

thickest layer of the heart composed of cardiac muscle cells built upon a framework of primarily collagenous fibers and blood vessels that supply it and the nervous fibers that help to regulate it

papillary muscle

extension of the myocardium in the ventricles to which the chordae tendineae attach

pectinate muscles

muscular ridges seen on the anterior surface of the right atrium

pericardial cavity

cavity surrounding the heart filled with a lubricating serous fluid that reduces friction as the heart contracts

pericardial sac

(also, pericardium) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium

pericardium

(also, pericardial sac) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium

posterior cardiac vein

vessel that parallels and drains the areas supplied by the marginal artery branch of the circumflex artery; drains into the great cardiac vein

posterior interventricular artery

(also, posterior descending artery) branch of the right coronary artery that runs along the posterior portion of the interventricular sulcus toward the apex of the heart and gives rise to branches that supply the interventricular septum and portions of both ventricles

posterior interventricular sulcus

sulcus located between the left and right ventricles on the anterior surface of the heart

pulmonary arteries

left and right branches of the pulmonary trunk that carry deoxygenated blood from the heart to each of the lungs

pulmonary capillaries

capillaries surrounding the alveoli of the lungs where gas exchange occurs: carbon dioxide exits the blood and oxygen enters

pulmonary circuit

blood flow to and from the lungs

pulmonary trunk

large arterial vessel that carries blood ejected from the right ventricle; divides into the left and right pulmonary arteries

pulmonary valve

(also, pulmonary semilunar valve, the pulmonic valve, or the right semilunar valve) valve at the base of the pulmonary trunk that prevents backflow of blood into the right ventricle; consists of three flaps

pulmonary veins

veins that carry highly oxygenated blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and to the many branches of the systemic circuit

right atrioventricular valve

(also, tricuspid valve) valve located between the right atrium and ventricle; consists of three flaps of tissue

semilunar valves

valves located at the base of the pulmonary trunk and at the base of the aorta

septum

(plural = septa) walls or partitions that divide the heart into chambers

septum primum

flap of tissue in the fetus that covers the foramen ovale within a few seconds after birth

small cardiac vein

parallels the right coronary artery and drains blood from the posterior surfaces of the right atrium and ventricle; drains into the great cardiac vein

sulcus

(plural = sulci) fat-filled groove visible on the surface of the heart; coronary vessels are also located in these areas

superior vena cava

large systemic vein that returns blood to the heart from the superior portion of the body

systemic circuit

blood flow to and from virtually all of the tissues of the body

trabeculae carneae

ridges of muscle covered by endocardium located in the ventricles

tricuspid valve

term used most often in clinical settings for the right atrioventricular valve

valve

in the cardiovascular system, a specialized structure located within the heart or vessels that ensures one-way flow of blood

ventricle

one of the primary pumping chambers of the heart located in the lower portion of the heart; the left ventricle is the major pumping chamber on the lower left side of the heart that ejects blood into the systemic circuit via the aorta and receives blood from the left atrium; the right ventricle is the major pumping chamber on the lower right side of the heart that ejects blood into the pulmonary circuit via the pulmonary trunk and receives blood from the right atrium

Cardiac Muscle and Electrical Activity

By the end of this section, you will be able to:

- Describe the structure of cardiac muscle
- Identify and describe the components of the conducting system that distributes electrical impulses through the heart
- Compare the effect of ion movement on membrane potential of cardiac conductive and contractile cells
- Relate characteristics of an electrocardiogram to events in the cardiac cycle
- Identify blocks that can interrupt the cardiac cycle

Recall that cardiac muscle shares a few characteristics with both skeletal muscle and smooth muscle, but it has some unique properties of its own. Not the least of these exceptional properties is its ability to initiate an electrical potential at a fixed rate that spreads rapidly from cell to cell to trigger the contractile mechanism. This property is known as **autorhythmicity**. Neither smooth nor skeletal muscle can do this. Even though cardiac muscle has autorhythmicity, heart rate is modulated by the endocrine and nervous systems.

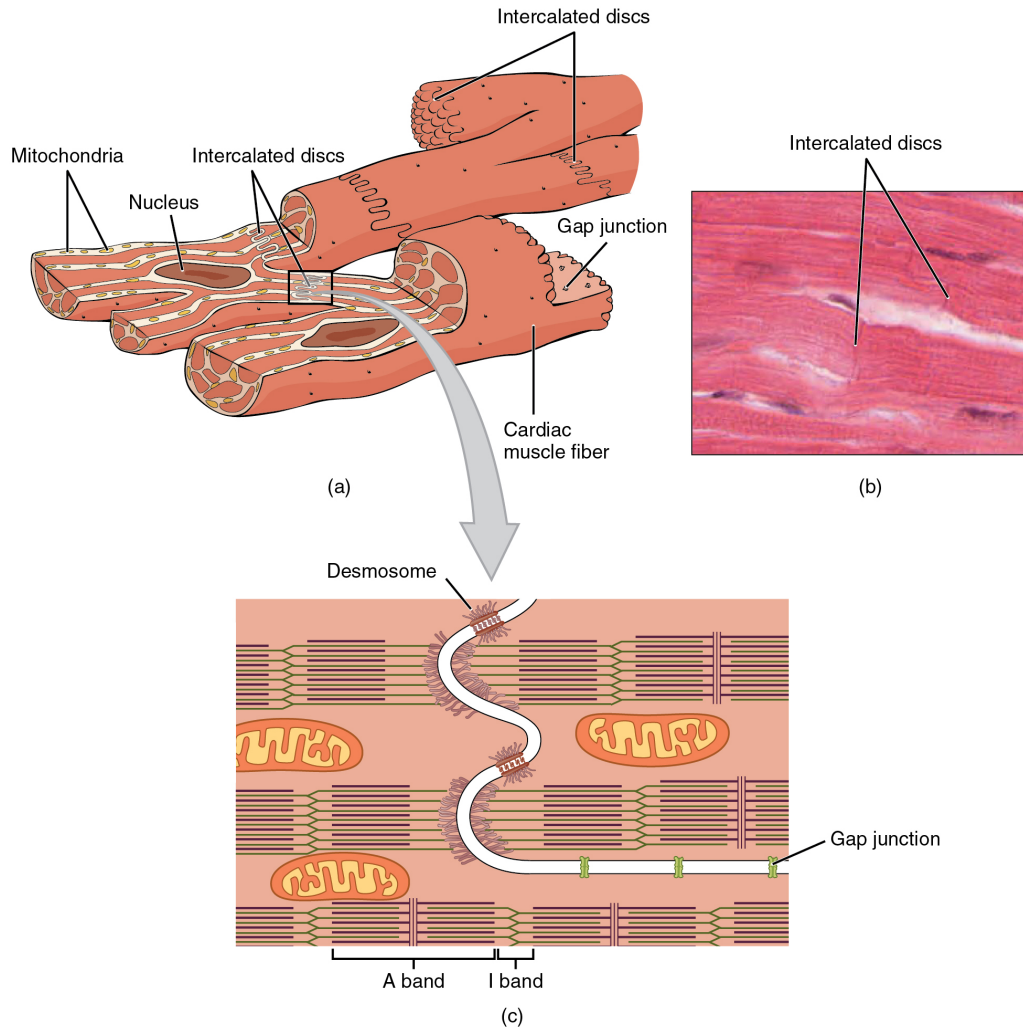
There are two major types of cardiac muscle cells: myocardial contractile cells and myocardial conducting cells. The **myocardial contractile cells** constitute the bulk (99 percent) of the cells in the atria and ventricles. Contractile cells conduct impulses and are responsible for contractions that pump blood through the body. The **myocardial conducting cells** (1 percent of the cells) form the conduction system of the heart. Except for Purkinje cells, they are generally much smaller than the contractile cells and have few of the myofibrils or filaments needed for contraction. Their function is similar in many respects to neurons, although they are specialized muscle cells. Myocardial conduction cells initiate and propagate the action potential (the electrical impulse) that travels throughout the heart and triggers the contractions that propel the blood.

Structure of Cardiac Muscle

Compared to the giant cylinders of skeletal muscle, cardiac muscle cells, or cardiomyocytes, are considerably shorter with much smaller diameters. Cardiac muscle also demonstrates striations, the alternating pattern of dark A bands and light I bands attributed to the precise arrangement of the myofilaments and fibrils that are organized in sarcomeres along the length of the cell ([\[link\]](#)a). These contractile elements are virtually identical to skeletal muscle. T (transverse) tubules penetrate from the surface plasma membrane, the sarcolemma, to the interior of the cell, allowing the electrical impulse to reach the interior. The T tubules are only found at the Z discs, whereas in skeletal muscle, they are found at the junction of the A and I bands. Therefore, there are one-half as many T tubules in cardiac muscle as in skeletal muscle. In addition, the sarcoplasmic reticulum stores few calcium ions, so most of the calcium ions must come from outside the cells. The result is a slower onset of contraction. Mitochondria are plentiful, providing energy for the contractions of the heart. Typically, cardiomyocytes have a single, central nucleus, but two or more nuclei may be found in some cells.

Cardiac muscle cells branch freely. A junction between two adjoining cells is marked by a critical structure called an **intercalated disc**, which helps support the synchronized contraction of the muscle ([\[link\]](#)b). The sarcolemmas from adjacent cells bind together at the intercalated discs. They consist of desmosomes, specialized linking proteoglycans, tight junctions, and large numbers of gap junctions that allow the passage of ions between the cells and help to synchronize the contraction ([\[link\]](#)c). Intercellular connective tissue also helps to bind the cells together. The importance of strongly binding these cells together is necessitated by the forces exerted by contraction.

Cardiac Muscle



(a) Cardiac muscle cells have myofibrils composed of myofilaments arranged in sarcomeres, T tubules to transmit the impulse from the sarcolemma to the interior of the cell, numerous mitochondria for energy, and intercalated discs that are found at the junction of different cardiac muscle cells. (b) A photomicrograph of cardiac muscle cells shows the nuclei and intercalated discs. (c) An intercalated disc connects cardiac muscle cells and consists of desmosomes and gap junctions. LM $\times 1600$. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Cardiac muscle undergoes aerobic respiration patterns, primarily metabolizing lipids and carbohydrates. Myoglobin, lipids, and glycogen are all stored within the cytoplasm. Cardiac muscle cells undergo twitch-type contractions with long refractory periods followed by brief relaxation periods. The relaxation is essential so the heart can fill with blood for the next cycle. The refractory period is very long to prevent the possibility of tetany, a condition in which muscle remains involuntarily contracted. In the heart, tetany is not compatible with life, since it would prevent the heart from pumping blood.

Note:

Everyday Connection

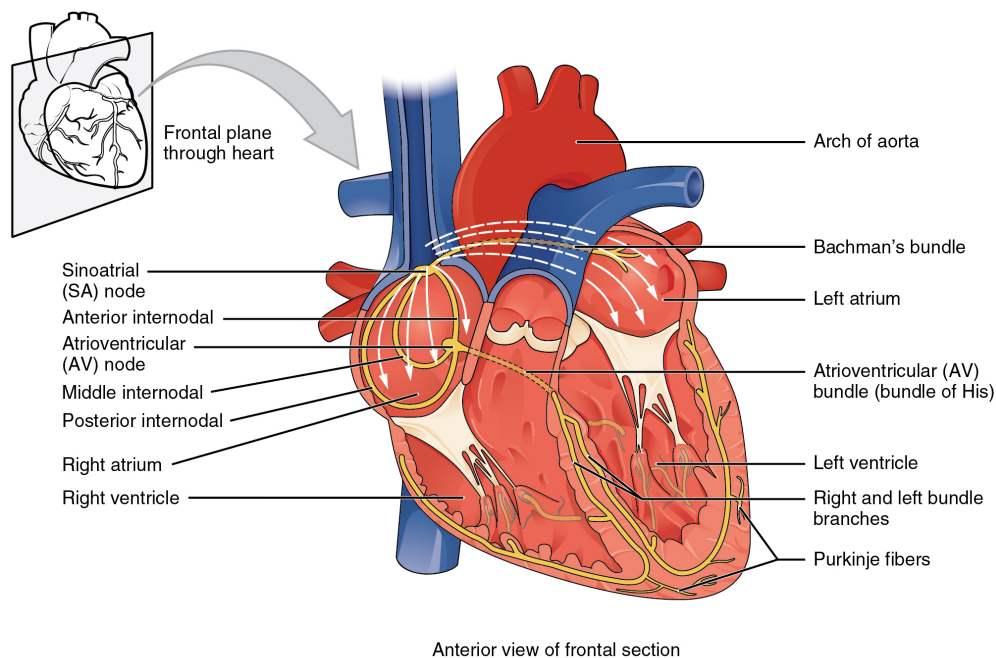
Repair and Replacement

Damaged cardiac muscle cells have extremely limited abilities to repair themselves or to replace dead cells via mitosis. Recent evidence indicates that at least some stem cells remain within the heart that continue to divide and at least potentially replace these dead cells. However, newly formed or repaired cells are rarely as functional as the original cells, and cardiac function is reduced. In the event of a heart attack or MI, dead cells are often replaced by patches of scar tissue. Autopsies performed on individuals who had successfully received heart transplants show some proliferation of original cells. If researchers can unlock the mechanism that generates new cells and restore full mitotic capabilities to heart muscle, the prognosis for heart attack survivors will be greatly enhanced. To date, myocardial cells produced within the patient (*in situ*) by cardiac stem cells seem to be nonfunctional, although those grown in Petri dishes (*in vitro*) do beat. Perhaps soon this mystery will be solved, and new advances in treatment will be commonplace.

Conduction System of the Heart

If embryonic heart cells are separated into a Petri dish and kept alive, each is capable of generating its own electrical impulse followed by contraction. When two independently beating embryonic cardiac muscle cells are placed

together, the cell with the higher inherent rate sets the pace, and the impulse spreads from the faster to the slower cell to trigger a contraction. As more cells are joined together, the fastest cell continues to assume control of the rate. A fully developed adult heart maintains the capability of generating its own electrical impulse, triggered by the fastest cells, as part of the cardiac conduction system. The components of the cardiac conduction system include the sinoatrial node, the atrioventricular node, the atrioventricular bundle, the atrioventricular bundle branches, and the Purkinje cells ([\[link\]](#)).
Conduction System of the Heart



Specialized conducting components of the heart include the sinoatrial node, the internodal pathways, the atrioventricular node, the atrioventricular bundle, the right and left bundle branches, and the Purkinje fibers.

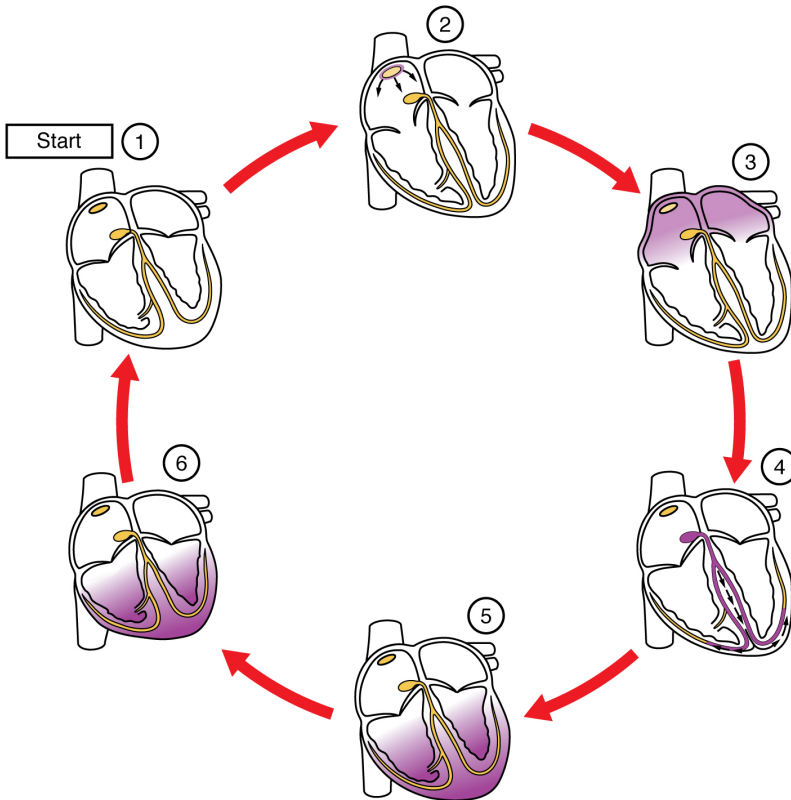
Sinoatrial (SA) Node

Normal cardiac rhythm is established by the **sinoatrial (SA) node**, a specialized clump of myocardial conducting cells located in the superior

and posterior walls of the right atrium in close proximity to the orifice of the superior vena cava. The SA node has the highest inherent rate of depolarization and is known as the **pacemaker** of the heart. It initiates the **sinus rhythm**, or normal electrical pattern followed by contraction of the heart.

This impulse spreads from its initiation in the SA node throughout the atria through specialized **internodal pathways**, to the atrial myocardial contractile cells and the atrioventricular node. The internodal pathways consist of three bands (anterior, middle, and posterior) that lead directly from the SA node to the next node in the conduction system, the atrioventricular node (see [\[link\]](#)). The impulse takes approximately 50 ms (milliseconds) to travel between these two nodes. The relative importance of this pathway has been debated since the impulse would reach the atrioventricular node simply following the cell-by-cell pathway through the contractile cells of the myocardium in the atria. In addition, there is a specialized pathway called **Bachmann's bundle** or the **interatrial band** that conducts the impulse directly from the right atrium to the left atrium. Regardless of the pathway, as the impulse reaches the atrioventricular septum, the connective tissue of the cardiac skeleton prevents the impulse from spreading into the myocardial cells in the ventricles except at the atrioventricular node. [\[link\]](#) illustrates the initiation of the impulse in the SA node that then spreads the impulse throughout the atria to the atrioventricular node.

Cardiac Conduction



- (1) The sinoatrial (SA) node and the remainder of the conduction system are at rest.
- (2) The SA node initiates the action potential, which sweeps across the atria.
- (3) After reaching the atrioventricular node, there is a delay of approximately 100 ms that allows the atria to complete pumping blood before the impulse is transmitted to the atrioventricular bundle.
- (4) Following the delay, the impulse travels through the atrioventricular bundle and bundle branches to the Purkinje fibers, and also reaches the right papillary muscle via the moderator band.
- (5) The impulse spreads to the contractile fibers of the ventricle.
- (6) Ventricular contraction begins.

The electrical event, the wave of depolarization, is the trigger for muscular contraction. The wave of depolarization begins in the right atrium, and the impulse spreads across the superior portions of both atria and then down through the contractile cells. The contractile cells then begin contraction from the superior to the inferior portions of the atria, efficiently pumping blood into the ventricles.

Atrioventricular (AV) Node

The **atrioventricular (AV) node** is a second clump of specialized myocardial conductive cells, located in the inferior portion of the right atrium within the atrioventricular septum. The septum prevents the impulse from spreading directly to the ventricles without passing through the AV node. There is a critical pause before the AV node depolarizes and transmits the impulse to the atrioventricular bundle (see [\[link\]](#), step 3). This delay in transmission is partially attributable to the small diameter of the cells of the node, which slow the impulse. Also, conduction between nodal cells is less efficient than between conducting cells. These factors mean that it takes the impulse approximately 100 ms to pass through the node. This pause is critical to heart function, as it allows the atrial cardiomyocytes to complete their contraction that pumps blood into the ventricles before the impulse is transmitted to the cells of the ventricle itself. With extreme stimulation by the SA node, the AV node can transmit impulses maximally at 220 per minute. This establishes the typical maximum heart rate in a healthy young individual. Damaged hearts or those stimulated by drugs can contract at higher rates, but at these rates, the heart can no longer effectively pump blood.

Atrioventricular Bundle (Bundle of His), Bundle Branches, and Purkinje Fibers

Arising from the AV node, the **atrioventricular bundle**, or **bundle of His**, proceeds through the interventricular septum before dividing into two **atrioventricular bundle branches**, commonly called the left and right

bundle branches. The left bundle branch has two fascicles. The left bundle branch supplies the left ventricle, and the right bundle branch the right ventricle. Since the left ventricle is much larger than the right, the left bundle branch is also considerably larger than the right. Portions of the right bundle branch are found in the moderator band and supply the right papillary muscles. Because of this connection, each papillary muscle receives the impulse at approximately the same time, so they begin to contract simultaneously just prior to the remainder of the myocardial contractile cells of the ventricles. This is believed to allow tension to develop on the chordae tendineae prior to right ventricular contraction. There is no corresponding moderator band on the left. Both bundle branches descend and reach the apex of the heart where they connect with the Purkinje fibers (see [\[link\]](#), step 4). This passage takes approximately 25 ms.

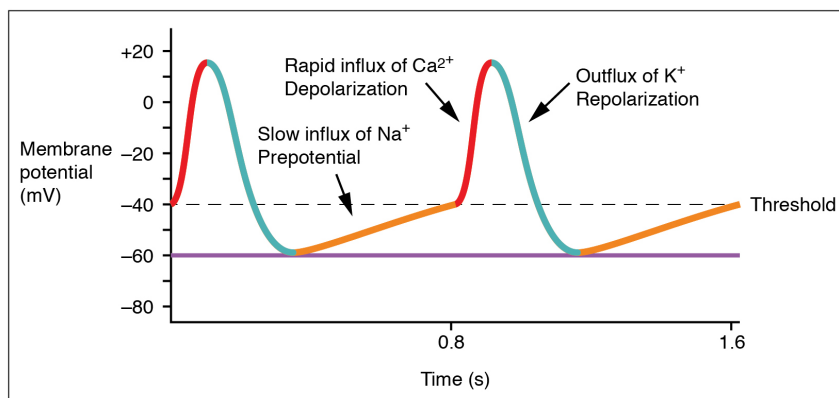
The **Purkinje fibers** are additional myocardial conductive fibers that spread the impulse to the myocardial contractile cells in the ventricles. They extend throughout the myocardium from the apex of the heart toward the atrioventricular septum and the base of the heart. The Purkinje fibers have a fast inherent conduction rate, and the electrical impulse reaches all of the ventricular muscle cells in about 75 ms (see [\[link\]](#), step 5). Since the electrical stimulus begins at the apex, the contraction also begins at the apex and travels toward the base of the heart, similar to squeezing a tube of toothpaste from the bottom. This allows the blood to be pumped out of the ventricles and into the aorta and pulmonary trunk. The total time elapsed from the initiation of the impulse in the SA node until depolarization of the ventricles is approximately 225 ms.

Membrane Potentials and Ion Movement in Cardiac Conductive Cells

Action potentials are considerably different between cardiac conductive cells and cardiac contractive cells. While Na^+ and K^+ play essential roles, Ca^{2+} is also critical for both types of cells. Unlike skeletal muscles and neurons, cardiac conductive cells do not have a stable resting potential. Conductive cells contain a series of sodium ion channels that allow a normal and slow influx of sodium ions that causes the membrane potential

to rise slowly from an initial value of -60 mV up to about -40 mV. The resulting movement of sodium ions creates **spontaneous depolarization** (or **prepotential depolarization**). At this point, calcium ion channels open and Ca^{2+} enters the cell, further depolarizing it at a more rapid rate until it reaches a value of approximately $+5$ mV. At this point, the calcium ion channels close and K^+ channels open, allowing outflux of K^+ and resulting in repolarization. When the membrane potential reaches approximately -60 mV, the K^+ channels close and Na^+ channels open, and the prepotential phase begins again. This phenomenon explains the autorhythmicity properties of cardiac muscle ([\[link\]](#)).

Action Potential at the SA Node



The prepotential is due to a slow influx of sodium ions until the threshold is reached followed by a rapid depolarization and repolarization. The prepotential accounts for the membrane reaching threshold and initiates the spontaneous depolarization and contraction of the cell. Note the lack of a resting potential.

Membrane Potentials and Ion Movement in Cardiac Contractile Cells

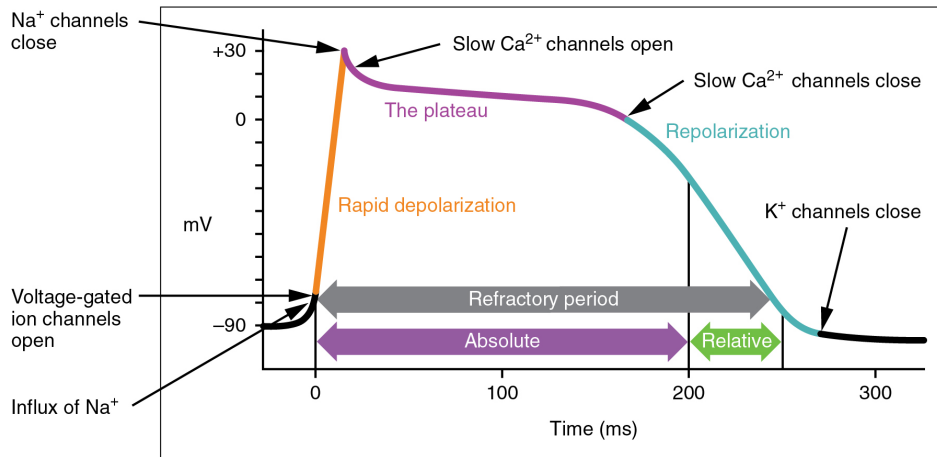
There is a distinctly different electrical pattern involving the contractile cells. In this case, there is a rapid depolarization, followed by a plateau

phase and then repolarization. This phenomenon accounts for the long refractory periods required for the cardiac muscle cells to pump blood effectively before they are capable of firing for a second time. These cardiac myocytes normally do not initiate their own electrical potential but rather wait for an impulse to reach them.

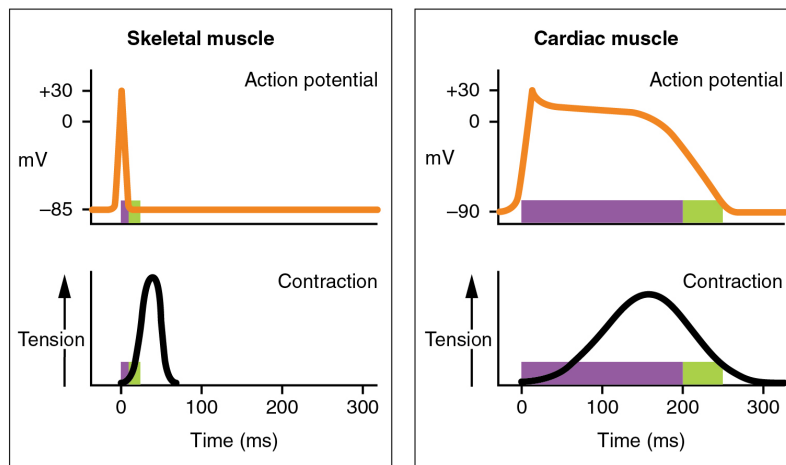
Contractile cells demonstrate a much more stable resting phase than conductive cells at approximately -80 mV for cells in the atria and -90 mV for cells in the ventricles. Despite this initial difference, the other components of their action potentials are virtually identical. In both cases, when stimulated by an action potential, voltage-gated channels rapidly open, beginning the positive-feedback mechanism of depolarization. This rapid influx of positively charged ions raises the membrane potential to approximately $+30$ mV, at which point the sodium channels close. The rapid depolarization period typically lasts 3–5 ms. Depolarization is followed by the plateau phase, in which membrane potential declines relatively slowly. This is due in large part to the opening of the slow Ca^{2+} channels, allowing Ca^{2+} to enter the cell while few K^{+} channels are open, allowing K^{+} to exit the cell. The relatively long plateau phase lasts approximately 175 ms. Once the membrane potential reaches approximately zero, the Ca^{2+} channels close and K^{+} channels open, allowing K^{+} to exit the cell. The repolarization lasts approximately 75 ms. At this point, membrane potential drops until it reaches resting levels once more and the cycle repeats. The entire event lasts between 250 and 300 ms ([link](#)).

The absolute refractory period for cardiac contractile muscle lasts approximately 200 ms, and the relative refractory period lasts approximately 50 ms, for a total of 250 ms. This extended period is critical, since the heart muscle must contract to pump blood effectively and the contraction must follow the electrical events. Without extended refractory periods, premature contractions would occur in the heart and would not be compatible with life.

Action Potential in Cardiac Contractile Cells



(a)



(b)

(a) Note the long plateau phase due to the influx of calcium ions. The extended refractory period allows the cell to fully contract before another electrical event can occur. (b) The action potential for heart muscle is compared to that of skeletal muscle.

Calcium Ions

Calcium ions play two critical roles in the physiology of cardiac muscle. Their influx through slow calcium channels accounts for the prolonged plateau phase and absolute refractory period that enable cardiac muscle to function properly. Calcium ions also combine with the regulatory protein troponin in the troponin-tropomyosin complex; this complex removes the inhibition that prevents the heads of the myosin molecules from forming cross bridges with the active sites on actin that provide the power stroke of contraction. This mechanism is virtually identical to that of skeletal muscle. Approximately 20 percent of the calcium required for contraction is supplied by the influx of Ca^{2+} during the plateau phase. The remaining Ca^{2+} for contraction is released from storage in the sarcoplasmic reticulum.

Comparative Rates of Conduction System Firing

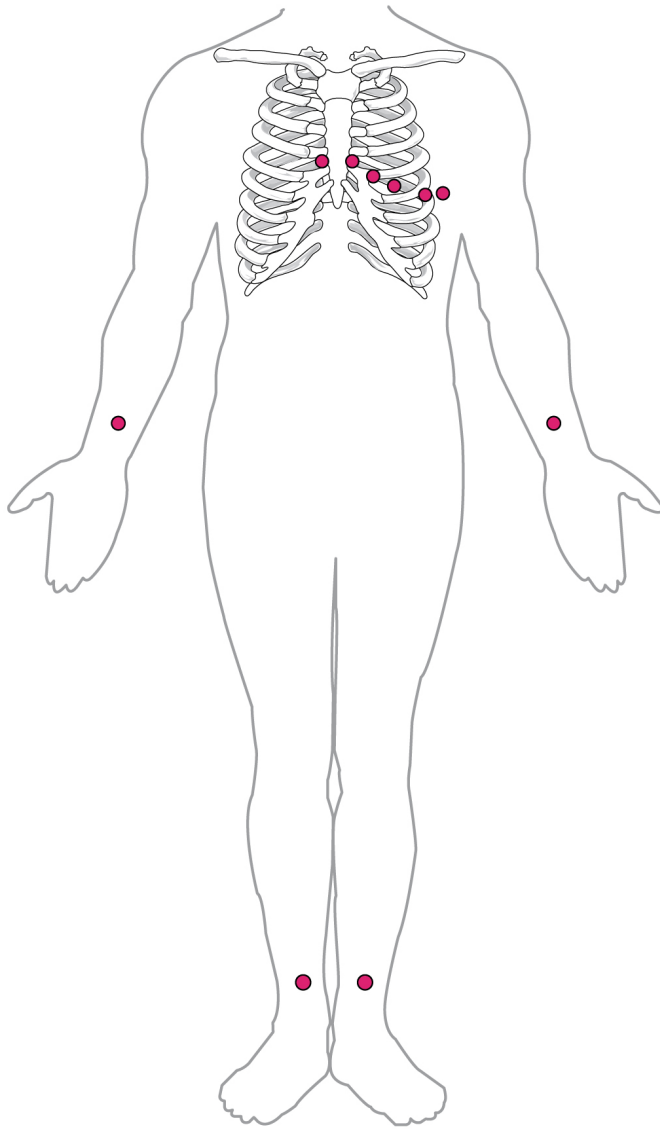
The pattern of prepotential or spontaneous depolarization, followed by rapid depolarization and repolarization just described, are seen in the SA node and a few other conductive cells in the heart. Since the SA node is the pacemaker, it reaches threshold faster than any other component of the conduction system. It will initiate the impulses spreading to the other conducting cells. The SA node, without nervous or endocrine control, would initiate a heart impulse approximately 80–100 times per minute. Although each component of the conduction system is capable of generating its own impulse, the rate progressively slows as you proceed from the SA node to the Purkinje fibers. Without the SA node, the AV node would generate a heart rate of 40–60 beats per minute. If the AV node were blocked, the atrioventricular bundle would fire at a rate of approximately 30–40 impulses per minute. The bundle branches would have an inherent rate of 20–30 impulses per minute, and the Purkinje fibers would fire at 15–20 impulses per minute. While a few exceptionally trained aerobic athletes demonstrate resting heart rates in the range of 30–40 beats per minute (the lowest recorded figure is 28 beats per minute for Miguel Indurain, a cyclist), for most individuals, rates lower than 50 beats per minute would indicate a condition called bradycardia. Depending upon the specific individual, as rates fall much below this level, the heart would be unable to maintain adequate flow of blood to vital tissues, initially resulting in

decreasing loss of function across the systems, unconsciousness, and ultimately death.

Electrocardiogram

By careful placement of surface electrodes on the body, it is possible to record the complex, compound electrical signal of the heart. This tracing of the electrical signal is the **electrocardiogram (ECG)**, also commonly abbreviated EKG (K coming kardiology, from the German term for cardiology). Careful analysis of the ECG reveals a detailed picture of both normal and abnormal heart function, and is an indispensable clinical diagnostic tool. The standard electrocardiograph (the instrument that generates an ECG) uses 3, 5, or 12 leads. The greater the number of leads an electrocardiograph uses, the more information the ECG provides. The term “lead” may be used to refer to the cable from the electrode to the electrical recorder, but it typically describes the voltage difference between two of the electrodes. The 12-lead electrocardiograph uses 10 electrodes placed in standard locations on the patient’s skin ([\[link\]](#)). In continuous ambulatory electrocardiographs, the patient wears a small, portable, battery-operated device known as a Holter monitor, or simply a Holter, that continuously monitors heart electrical activity, typically for a period of 24 hours during the patient’s normal routine.

Standard Placement of ECG Leads



In a 12-lead ECG, six electrodes are placed on the chest, and four electrodes are placed on the limbs.

A normal ECG tracing is presented in [\[link\]](#). Each component, segment, and interval is labeled and corresponds to important electrical events, demonstrating the relationship between these events and contraction in the heart.

There are five prominent points on the ECG: the P wave, the QRS complex, and the T wave. The small **P wave** represents the depolarization of the atria. The atria begin contracting approximately 25 ms after the start of the P wave. The large **QRS complex** represents the depolarization of the ventricles, which requires a much stronger electrical signal because of the larger size of the ventricular cardiac muscle. The ventricles begin to contract as the QRS reaches the peak of the R wave. Lastly, the **T wave** represents the repolarization of the ventricles. The repolarization of the atria occurs during the QRS complex, which masks it on an ECG.

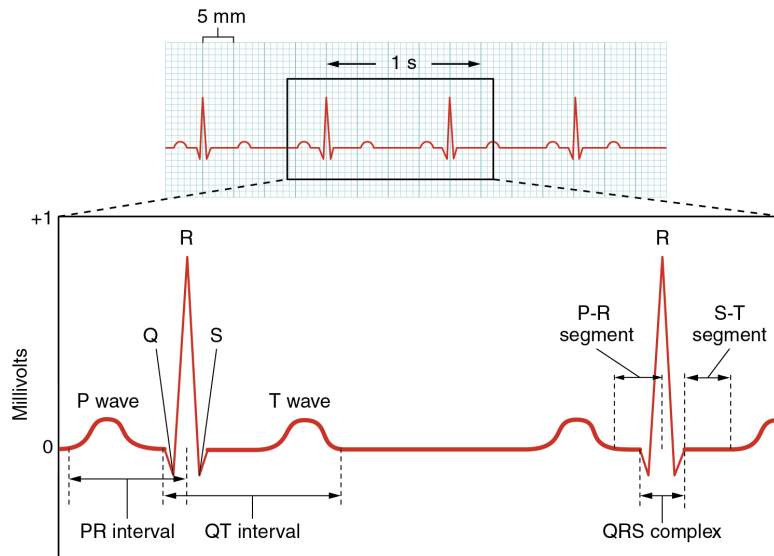
The major segments and intervals of an ECG tracing are indicated in [\[link\]](#). Segments are defined as the regions between two waves. Intervals include one segment plus one or more waves. For example, the PR segment begins at the end of the P wave and ends at the beginning of the QRS complex. The PR interval starts at the beginning of the P wave and ends with the beginning of the QRS complex. The PR interval is more clinically relevant, as it measures the duration from the beginning of atrial depolarization (the P wave) to the initiation of the QRS complex. Since the Q wave may be difficult to view in some tracings, the measurement is often extended to the R that is more easily visible. Should there be a delay in passage of the impulse from the SA node to the AV node, it would be visible in the PR interval. [\[link\]](#) correlates events of heart contraction to the corresponding segments and intervals of an ECG.

Note:



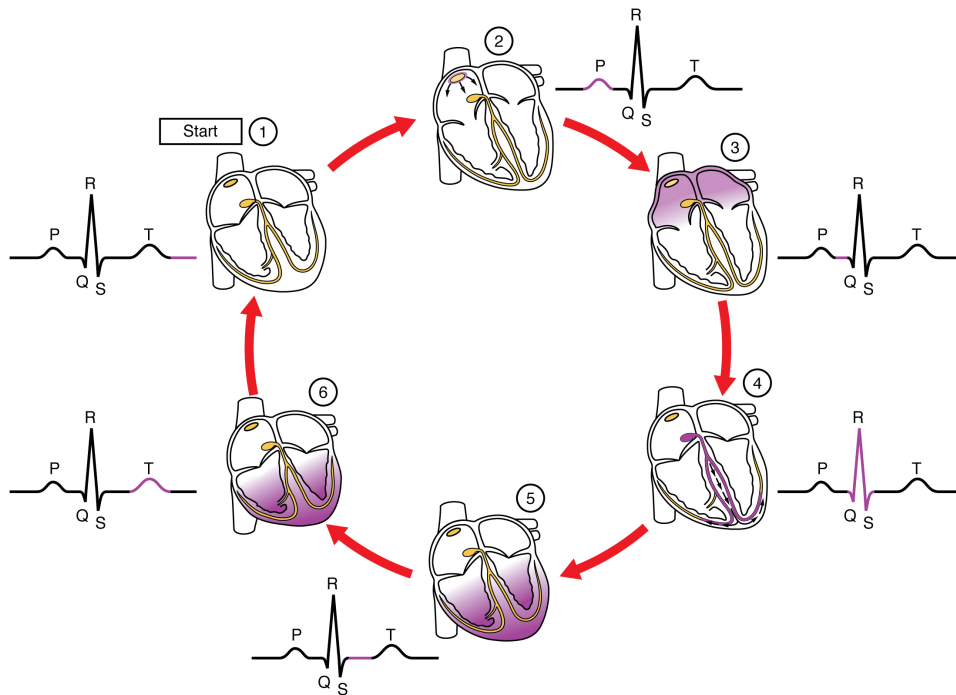
Visit this [site](#) for a more detailed analysis of ECGs.

Electrocardiogram



A normal tracing shows the P wave, QRS complex, and T wave. Also indicated are the PR, QT, QRS, and ST intervals, plus the P-R and S-T segments.

ECG Tracing Correlated to the Cardiac Cycle



This diagram correlates an ECG tracing with the electrical and mechanical events of a heart contraction. Each segment of an ECG tracing corresponds to one event in the cardiac cycle.

Note:

Everyday Connection

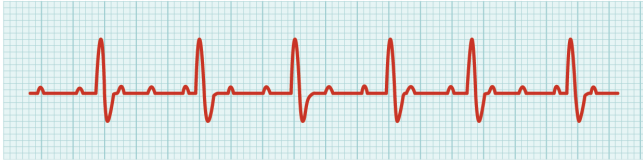
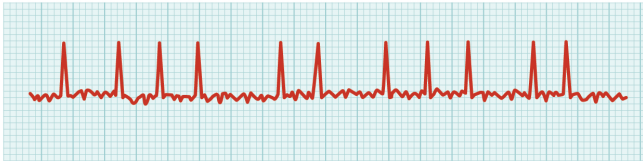
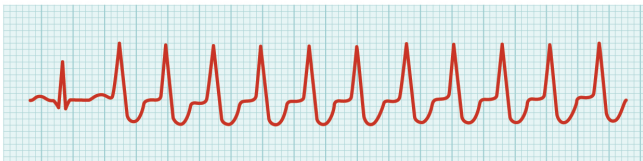
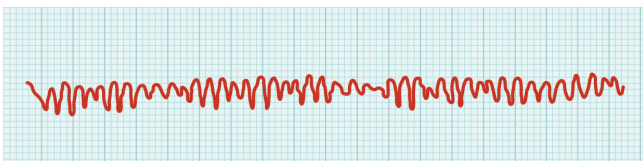

ECG Abnormalities

Occasionally, an area of the heart other than the SA node will initiate an impulse that will be followed by a premature contraction. Such an area, which may actually be a component of the conduction system or some other contractile cells, is known as an ectopic focus or ectopic pacemaker. An ectopic focus may be stimulated by localized ischemia; exposure to certain drugs, including caffeine, digitalis, or acetylcholine; elevated stimulation by both sympathetic or parasympathetic divisions of the autonomic nervous system; or a number of disease or pathological conditions. Occasional occurrences are generally transitory and nonlife threatening, but if the condition becomes chronic, it may lead to either an arrhythmia, a deviation from the normal pattern of impulse conduction and contraction, or to fibrillation, an uncoordinated beating of the heart.

While interpretation of an ECG is possible and extremely valuable after some training, a full understanding of the complexities and intricacies generally requires several years of experience. In general, the size of the electrical variations, the duration of the events, and detailed vector analysis provide the most comprehensive picture of cardiac function. For example, an amplified P wave may indicate enlargement of the atria, an enlarged Q wave may indicate a MI, and an enlarged suppressed or inverted Q wave often indicates enlarged ventricles. T waves often appear flatter when insufficient oxygen is being delivered to the myocardium. An elevation of the ST segment above baseline is often seen in patients with an acute MI, and may appear depressed below the baseline when hypoxia is occurring. As useful as analyzing these electrical recordings may be, there are limitations. For example, not all areas suffering a MI may be obvious on

the ECG. Additionally, it will not reveal the effectiveness of the pumping, which requires further testing, such as an ultrasound test called an echocardiogram or nuclear medicine imaging. It is also possible for there to be pulseless electrical activity, which will show up on an ECG tracing, although there is no corresponding pumping action. Common abnormalities that may be detected by the ECGs are shown in [\[link\]](#).

Common ECG Abnormalities

- | | |
|--|---|
|  <p>(a) Second-degree (partial) block</p> | <p>Note how half of the P waves are not followed by the QRS complex and T waves while the other half are. Question: What would you expect to happen to heart rate (pulse)?</p> |
|  <p>(b) Atrial fibrillation</p> | <p>Note the abnormal electrical pattern prior to the QRS complexes. Also note how the frequency between the QRS complexes has increased. Question: What would you expect to happen to heart rate (pulse)?</p> |
|  <p>(c) Ventricular tachycardia</p> | <p>Note the unusual shape of the QRS complex, focusing on the "S" component. Question: What would you expect to happen to heart rate (pulse)?</p> |
|  <p>(d) Ventricular fibrillation</p> | <p>Note the total lack of normal electrical activity. Question: What would you expect to happen to heart rate (pulse)?</p> |
|  <p>(e) Third-degree block</p> | <p>Note that in a third-degree block some of the impulses initiated by the SA node do not reach the AV node while others do. Also note that the P waves are not followed by the QRS complex. Question: What would you expect to happen to heart rate (pulse)?</p> |

(a) In a second-degree or partial block, one-half of the P waves are not followed by the QRS complex and T waves while the other half are. (b) In atrial fibrillation, the electrical pattern is abnormal prior to the QRS complex, and the frequency between the QRS complexes has increased. (c) In ventricular tachycardia, the shape of the

QRS complex is abnormal. (d) In ventricular fibrillation, there is no normal electrical activity. (e) In a third-degree block, there is no correlation between atrial activity (the P wave) and ventricular activity (the QRS complex).

Note:



Visit this [site](#) for a more complete library of abnormal ECGs.

Note:

Everyday Connection

External Automated Defibrillators

In the event that the electrical activity of the heart is severely disrupted, cessation of electrical activity or fibrillation may occur. In fibrillation, the heart beats in a wild, uncontrolled manner, which prevents it from being able to pump effectively. Atrial fibrillation (see [\[link\]](#)**b**) is a serious condition, but as long as the ventricles continue to pump blood, the patient's life may not be in immediate danger. Ventricular fibrillation (see [\[link\]](#)**d**) is a medical emergency that requires life support, because the ventricles are not effectively pumping blood. In a hospital setting, it is often described as “code blue.” If untreated for as little as a few minutes, ventricular fibrillation may lead to brain death. The most common treatment is defibrillation, which uses special paddles to apply a charge to the heart from an external electrical source in an attempt to establish a normal sinus rhythm ([\[link\]](#)). A defibrillator effectively stops the heart so

that the SA node can trigger a normal conduction cycle. Because of their effectiveness in reestablishing a normal sinus rhythm, external automated defibrillators (EADs) are being placed in areas frequented by large numbers of people, such as schools, restaurants, and airports. These devices contain simple and direct verbal instructions that can be followed by nonmedical personnel in an attempt to save a life.

Defibrillators



(a)



(b)

(a) An external automatic defibrillator can be used by nonmedical personnel to reestablish a normal sinus rhythm in a person with fibrillation. (b) Defibrillator paddles are more commonly used in hospital settings. (credit b: "widerider107"/flickr.com)

A **heart block** refers to an interruption in the normal conduction pathway. The nomenclature for these is very straightforward. SA nodal blocks occur within the SA node. AV nodal blocks occur within the AV node. Infra-Hisian blocks involve the bundle of His. Bundle branch blocks occur within either the left or right atrioventricular bundle branches. Hemiblocks are partial and occur within one or more fascicles of the atrioventricular bundle branch. Clinically, the most common types are the AV nodal and infra-Hisian blocks.

AV blocks are often described by degrees. A first-degree or partial block indicates a delay in conduction between the SA and AV nodes. This can be recognized on the ECG as an abnormally long PR interval. A second-degree or incomplete block occurs when some impulses from the SA node reach the AV node and continue, while others do not. In this instance, the ECG would reveal some P waves not followed by a QRS complex, while others would appear normal. In the third-degree or complete block, there is no correlation between atrial activity (the P wave) and ventricular activity (the QRS complex). Even in the event of a total SA block, the AV node will assume the role of pacemaker and continue initiating contractions at 40–60 contractions per minute, which is adequate to maintain consciousness. Second- and third-degree blocks are demonstrated on the ECG presented in [\[link\]](#).

When arrhythmias become a chronic problem, the heart maintains a junctional rhythm, which originates in the AV node. In order to speed up the heart rate and restore full sinus rhythm, a cardiologist can implant an **artificial pacemaker**, which delivers electrical impulses to the heart muscle to ensure that the heart continues to contract and pump blood effectively. These artificial pacemakers are programmable by the cardiologists and can either provide stimulation temporarily upon demand or on a continuous basis. Some devices also contain built-in defibrillators.

Cardiac Muscle Metabolism

Normally, cardiac muscle metabolism is entirely aerobic. Oxygen from the lungs is brought to the heart, and every other organ, attached to the hemoglobin molecules within the erythrocytes. Heart cells also store appreciable amounts of oxygen in myoglobin. Normally, these two mechanisms, circulating oxygen and oxygen attached to myoglobin, can supply sufficient oxygen to the heart, even during peak performance.

Fatty acids and glucose from the circulation are broken down within the mitochondria to release energy in the form of ATP. Both fatty acid droplets and glycogen are stored within the sarcoplasm and provide additional nutrient supply. (Seek additional content for more detail about metabolism.)

Chapter Review

The heart is regulated by both neural and endocrine control, yet it is capable of initiating its own action potential followed by muscular contraction. The conductive cells within the heart establish the heart rate and transmit it through the myocardium. The contractile cells contract and propel the blood. The normal path of transmission for the conductive cells is the sinoatrial (SA) node, internodal pathways, atrioventricular (AV) node, atrioventricular (AV) bundle of His, bundle branches, and Purkinje fibers. The action potential for the conductive cells consists of a prepotential phase with a slow influx of Na^+ followed by a rapid influx of Ca^{2+} and outflux of K^+ . Contractile cells have an action potential with an extended plateau phase that results in an extended refractory period to allow complete contraction for the heart to pump blood effectively. Recognizable points on the ECG include the P wave that corresponds to atrial depolarization, the QRS complex that corresponds to ventricular depolarization, and the T wave that corresponds to ventricular repolarization.

Review Questions

Exercise:

Problem: Which of the following is unique to cardiac muscle cells?

- a. Only cardiac muscle contains a sarcoplasmic reticulum.
- b. Only cardiac muscle has gap junctions.
- c. Only cardiac muscle is capable of autorhythmicity
- d. Only cardiac muscle has a high concentration of mitochondria.

Solution:

C

Exercise:

Problem: The influx of which ion accounts for the plateau phase?

- a. sodium
- b. potassium
- c. chloride
- d. calcium

Solution:

D

Exercise:

Problem:

Which portion of the ECG corresponds to repolarization of the atria?

- a. P wave
- b. QRS complex
- c. T wave
- d. none of the above: atrial repolarization is masked by ventricular depolarization

Solution:

D

Exercise:

Problem:

Which component of the heart conduction system would have the slowest rate of firing?

- a. atrioventricular node
- b. atrioventricular bundle
- c. bundle branches
- d. Purkinje fibers

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

Why is the plateau phase so critical to cardiac muscle function?

Solution:

It prevents additional impulses from spreading through the heart prematurely, thereby allowing the muscle sufficient time to contract and pump blood effectively.

Exercise:

Problem:

How does the delay of the impulse at the atrioventricular node contribute to cardiac function?

Solution:

It ensures sufficient time for the atrial muscle to contract and pump blood into the ventricles prior to the impulse being conducted into the lower chambers.

Exercise:

Problem:

How do gap junctions and intercalated disks aid contraction of the heart?

Solution:

Gap junctions within the intercalated disks allow impulses to spread from one cardiac muscle cell to another, allowing sodium, potassium,

and calcium ions to flow between adjacent cells, propagating the action potential, and ensuring coordinated contractions.

Exercise:

Problem:

Why do the cardiac muscles cells demonstrate autorhythmicity?

Solution:

Without a true resting potential, there is a slow influx of sodium ions through slow channels that produces a prepotential that gradually reaches threshold.

Glossary

artificial pacemaker

medical device that transmits electrical signals to the heart to ensure that it contracts and pumps blood to the body

atrioventricular bundle

(also, bundle of His) group of specialized myocardial conductile cells that transmit the impulse from the AV node through the interventricular septum; form the left and right atrioventricular bundle branches

atrioventricular bundle branches

(also, left or right bundle branches) specialized myocardial conductile cells that arise from the bifurcation of the atrioventricular bundle and pass through the interventricular septum; lead to the Purkinje fibers and also to the right papillary muscle via the moderator band

atrioventricular (AV) node

clump of myocardial cells located in the inferior portion of the right atrium within the atrioventricular septum; receives the impulse from the SA node, pauses, and then transmits it into specialized conducting cells within the interventricular septum

autorhythmicity

ability of cardiac muscle to initiate its own electrical impulse that triggers the mechanical contraction that pumps blood at a fixed pace without nervous or endocrine control

Bachmann's bundle

(also, interatrial band) group of specialized conducting cells that transmit the impulse directly from the SA node in the right atrium to the left atrium

bundle of His

(also, atrioventricular bundle) group of specialized myocardial conductile cells that transmit the impulse from the AV node through the interventricular septum; form the left and right atrioventricular bundle branches

electrocardiogram (ECG)

surface recording of the electrical activity of the heart that can be used for diagnosis of irregular heart function; also abbreviated as EKG

heart block

interruption in the normal conduction pathway

interatrial band

(also, Bachmann's bundle) group of specialized conducting cells that transmit the impulse directly from the SA node in the right atrium to the left atrium

intercalated disc

physical junction between adjacent cardiac muscle cells; consisting of desmosomes, specialized linking proteoglycans, and gap junctions that allow passage of ions between the two cells

internodal pathways

specialized conductile cells within the atria that transmit the impulse from the SA node throughout the myocardial cells of the atrium and to the AV node

myocardial conducting cells

specialized cells that transmit electrical impulses throughout the heart and trigger contraction by the myocardial contractile cells

myocardial contractile cells

bulk of the cardiac muscle cells in the atria and ventricles that conduct impulses and contract to propel blood

P wave

component of the electrocardiogram that represents the depolarization of the atria

pacemaker

cluster of specialized myocardial cells known as the SA node that initiates the sinus rhythm

prepotential depolarization

(also, spontaneous depolarization) mechanism that accounts for the autorhythmic property of cardiac muscle; the membrane potential increases as sodium ions diffuse through the always-open sodium ion channels and causes the electrical potential to rise

Purkinje fibers

specialized myocardial conduction fibers that arise from the bundle branches and spread the impulse to the myocardial contraction fibers of the ventricles

QRS complex

component of the electrocardiogram that represents the depolarization of the ventricles and includes, as a component, the repolarization of the atria

sinoatrial (SA) node

known as the pacemaker, a specialized clump of myocardial conducting cells located in the superior portion of the right atrium that has the highest inherent rate of depolarization that then spreads throughout the heart

sinus rhythm

normal contractile pattern of the heart

spontaneous depolarization

(also, prepotential depolarization) the mechanism that accounts for the autorhythmic property of cardiac muscle; the membrane potential increases as sodium ions diffuse through the always-open sodium ion channels and causes the electrical potential to rise

T wave

component of the electrocardiogram that represents the repolarization of the ventricles

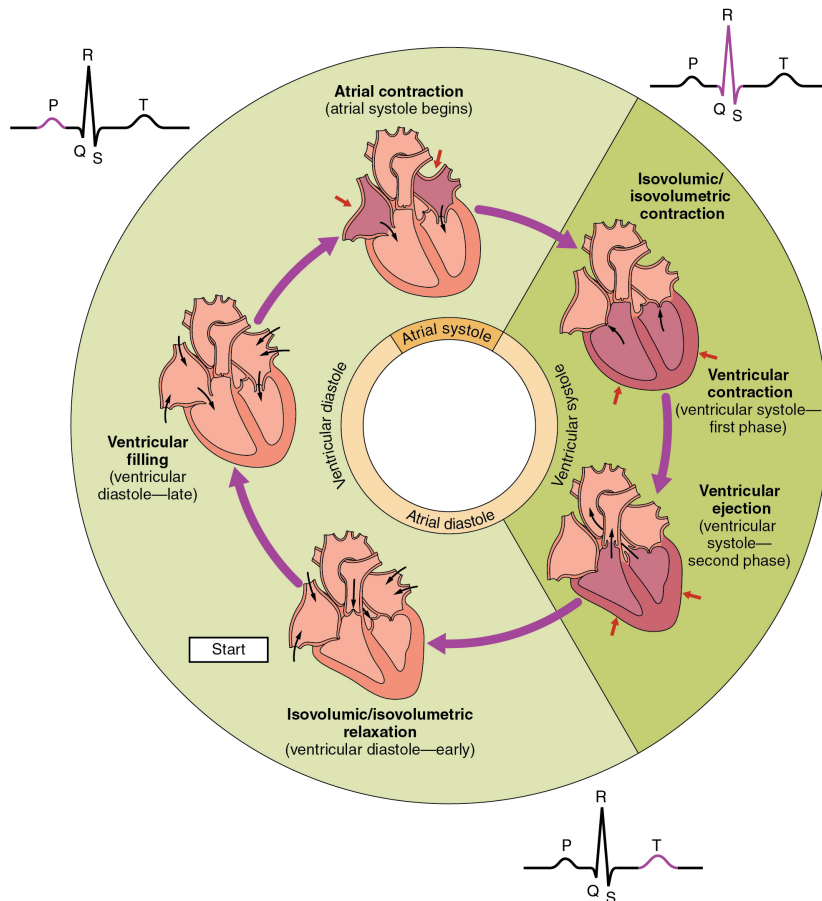
Cardiac Cycle

By the end of this section, you will be able to:

- Describe the relationship between blood pressure and blood flow
- Summarize the events of the cardiac cycle
- Compare atrial and ventricular systole and diastole
- Relate heart sounds detected by auscultation to action of heart's valves

The period of time that begins with contraction of the atria and ends with ventricular relaxation is known as the **cardiac cycle** ([\[link\]](#)). The period of contraction that the heart undergoes while it pumps blood into circulation is called **systole**. The period of relaxation that occurs as the chambers fill with blood is called **diastole**. Both the atria and ventricles undergo systole and diastole, and it is essential that these components be carefully regulated and coordinated to ensure blood is pumped efficiently to the body.

Overview of the Cardiac Cycle



The cardiac cycle begins with atrial systole and progresses to ventricular systole, atrial diastole, and ventricular diastole, when the cycle begins again. Correlations to the ECG are highlighted.

Pressures and Flow

Fluids, whether gases or liquids, are materials that flow according to pressure gradients—that is, they move from regions that are higher in pressure to regions that are lower in pressure. Accordingly, when the heart chambers are relaxed (diastole), blood will flow into the atria from the veins, which are higher in pressure. As blood flows into the atria, the pressure will rise, so the blood will initially move passively from the atria into the ventricles. When the action potential triggers the muscles in the atria to contract (atrial systole), the pressure within the atria rises further, pumping blood into the ventricles. During ventricular systole, pressure rises in the ventricles, pumping blood into the pulmonary trunk from the right ventricle and into the aorta from the left ventricle. Again, as you consider this flow and relate it to the conduction pathway, the elegance of the system should become apparent.

Phases of the Cardiac Cycle

At the beginning of the cardiac cycle, both the atria and ventricles are relaxed (diastole). Blood is flowing into the right atrium from the superior and inferior venae cavae and the coronary sinus. Blood flows into the left atrium from the four pulmonary veins. The two atrioventricular valves, the tricuspid and mitral valves, are both open, so blood flows unimpeded from the atria and into the ventricles. Approximately 70–80 percent of ventricular filling occurs by this method. The two semilunar valves, the pulmonary and aortic valves, are closed, preventing backflow of blood into the right and left ventricles from the pulmonary trunk on the right and the aorta on the left.

Atrial Systole and Diastole

Contraction of the atria follows depolarization, represented by the P wave of the ECG. As the atrial muscles contract from the superior portion of the atria toward the atrioventricular septum, pressure rises within the atria and blood is pumped into the ventricles through the open atrioventricular (tricuspid, and mitral or bicuspid) valves. At the start of atrial systole, the ventricles are normally filled with approximately 70–80 percent of their capacity due to inflow during diastole. Atrial contraction, also referred to as the “atrial kick,” contributes the remaining 20–30 percent of filling (see [\[link\]](#)). Atrial systole lasts approximately 100 ms and ends prior to ventricular systole, as the atrial muscle returns to diastole.

Ventricular Systole

Ventricular systole (see [\[link\]](#)) follows the depolarization of the ventricles and is represented by the QRS complex in the ECG. It may be conveniently divided into two phases, lasting a total of 270 ms. At the end of atrial systole and just prior to atrial contraction, the ventricles contain approximately 130 mL blood in a resting adult in a standing position. This volume is known as the **end diastolic volume (EDV)** or **preload**.

Initially, as the muscles in the ventricle contract, the pressure of the blood within the chamber rises, but it is not yet high enough to open the semilunar (pulmonary and aortic) valves and be ejected from the heart. However, blood pressure quickly rises above that of the atria that are now relaxed and in diastole. This increase in pressure causes blood to flow back toward the atria, closing the tricuspid and mitral valves. Since blood is not being ejected from the ventricles at this early stage, the volume of blood within the chamber remains constant. Consequently, this initial phase of ventricular systole is known as **isovolumic contraction**, also called isovolumetric contraction (see [\[link\]](#)).

In the second phase of ventricular systole, the **ventricular ejection phase**, the contraction of the ventricular muscle has raised the pressure within the ventricle to the point that it is greater than the pressures in the pulmonary

trunk and the aorta. Blood is pumped from the heart, pushing open the pulmonary and aortic semilunar valves. Pressure generated by the left ventricle will be appreciably greater than the pressure generated by the right ventricle, since the existing pressure in the aorta will be so much higher. Nevertheless, both ventricles pump the same amount of blood. This quantity is referred to as stroke volume. Stroke volume will normally be in the range of 70–80 mL. Since ventricular systole began with an EDV of approximately 130 mL of blood, this means that there is still 50–60 mL of blood remaining in the ventricle following contraction. This volume of blood is known as the **end systolic volume (ESV)**.

Ventricular Diastole

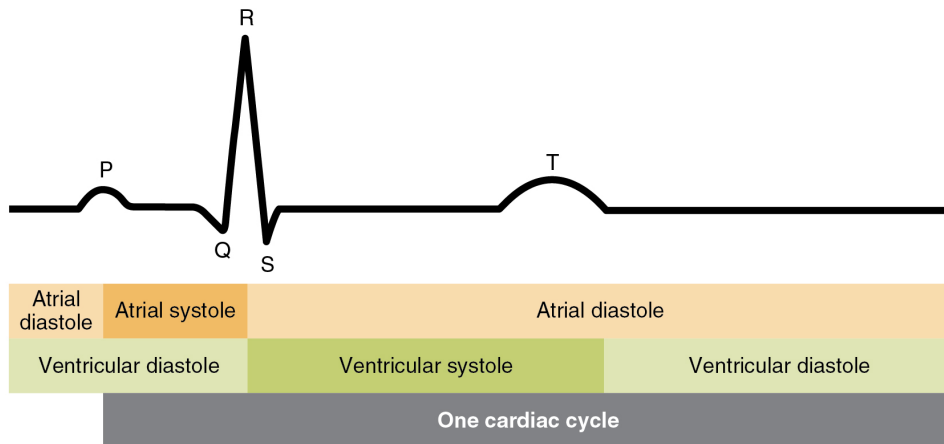
Ventricular relaxation, or diastole, follows repolarization of the ventricles and is represented by the T wave of the ECG. It too is divided into two distinct phases and lasts approximately 430 ms.

During the early phase of ventricular diastole, as the ventricular muscle relaxes, pressure on the remaining blood within the ventricle begins to fall. When pressure within the ventricles drops below pressure in both the pulmonary trunk and aorta, blood flows back toward the heart, producing the dicrotic notch (small dip) seen in blood pressure tracings. The semilunar valves close to prevent backflow into the heart. Since the atrioventricular valves remain closed at this point, there is no change in the volume of blood in the ventricle, so the early phase of ventricular diastole is called the **isovolumic ventricular relaxation phase**, also called isovolumetric ventricular relaxation phase (see [\[link\]](#)).

In the second phase of ventricular diastole, called late ventricular diastole, as the ventricular muscle relaxes, pressure on the blood within the ventricles drops even further. Eventually, it drops below the pressure in the atria. When this occurs, blood flows from the atria into the ventricles, pushing open the tricuspid and mitral valves. As pressure drops within the ventricles, blood flows from the major veins into the relaxed atria and from there into the ventricles. Both chambers are in diastole, the atrioventricular

valves are open, and the semilunar valves remain closed (see [\[link\]](#)). The cardiac cycle is complete.

[\[link\]](#) illustrates the relationship between the cardiac cycle and the ECG. Relationship between the Cardiac Cycle and ECG



Initially, both the atria and ventricles are relaxed (diastole). The P wave represents depolarization of the atria and is followed by atrial contraction (systole). Atrial systole extends until the QRS complex, at which point, the atria relax. The QRS complex represents depolarization of the ventricles and is followed by ventricular contraction. The T wave represents the repolarization of the ventricles and marks the beginning of ventricular relaxation.

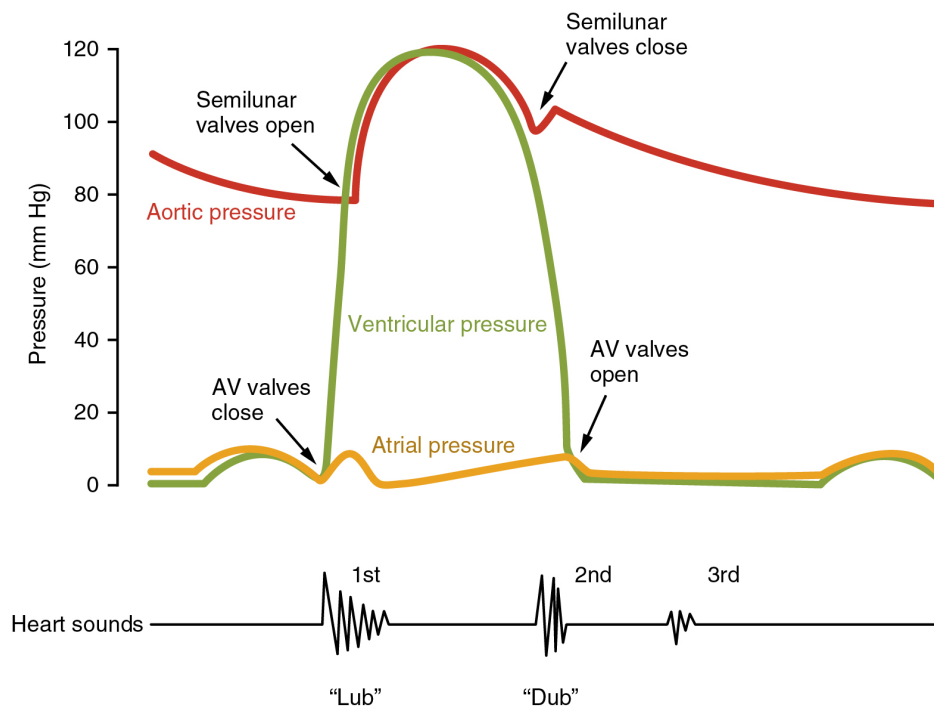
Heart Sounds

One of the simplest, yet effective, diagnostic techniques applied to assess the state of a patient's heart is auscultation using a stethoscope.

In a normal, healthy heart, there are only two audible **heart sounds**: S_1 and S_2 . S_1 is the sound created by the closing of the atrioventricular valves during ventricular contraction and is normally described as a “lub,” or first heart sound. The second heart sound, S_2 , is the sound of the closing of the

semilunar valves during ventricular diastole and is described as a “dub” ([link](#)). In both cases, as the valves close, the openings within the atrioventricular septum guarded by the valves will become reduced, and blood flow through the opening will become more turbulent until the valves are fully closed. There is a third heart sound, S_3 , but it is rarely heard in healthy individuals. It may be the sound of blood flowing into the atria, or blood sloshing back and forth in the ventricle, or even tensing of the chordae tendineae. S_3 may be heard in youth, some athletes, and pregnant women. If the sound is heard later in life, it may indicate congestive heart failure, warranting further tests. Some cardiologists refer to the collective S_1 , S_2 , and S_3 sounds as the “Kentucky gallop,” because they mimic those produced by a galloping horse. The fourth heart sound, S_4 , results from the contraction of the atria pushing blood into a stiff or hypertrophic ventricle, indicating failure of the left ventricle. S_4 occurs prior to S_1 and the collective sounds S_4 , S_1 , and S_2 are referred to by some cardiologists as the “Tennessee gallop,” because of their similarity to the sound produced by a galloping horse with a different gait. A few individuals may have both S_3 and S_4 , and this combined sound is referred to as S_7 .

Heart Sounds and the Cardiac Cycle



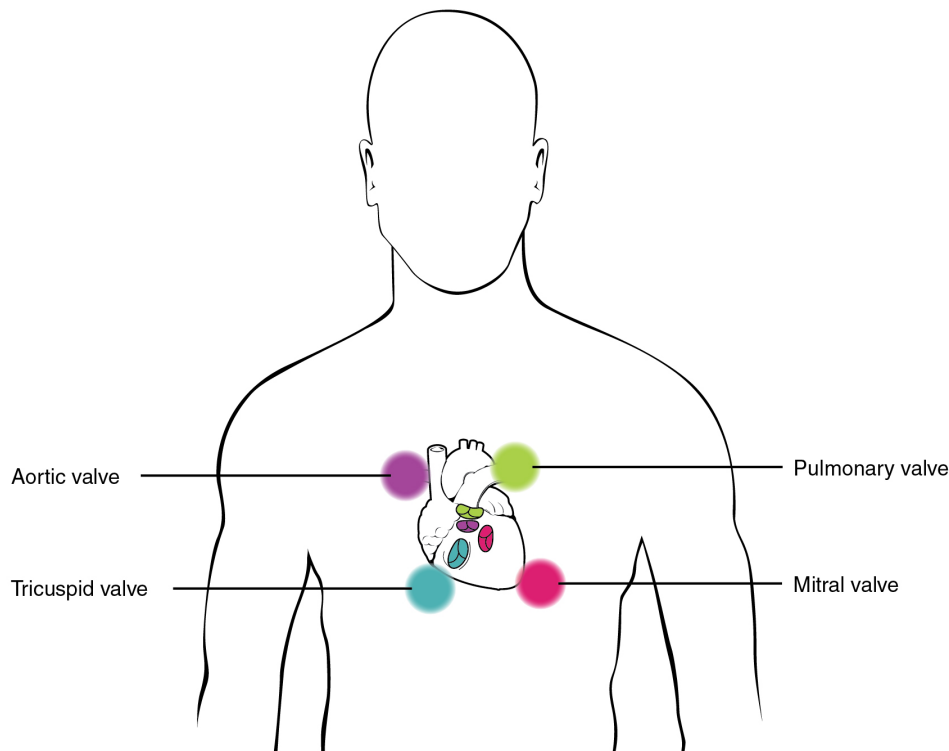
In this illustration, the x-axis reflects time with a

recording of the heart sounds. The y-axis represents pressure.

The term **murmur** is used to describe an unusual sound coming from the heart that is caused by the turbulent flow of blood. Murmurs are graded on a scale of 1 to 6, with 1 being the most common, the most difficult sound to detect, and the least serious. The most severe is a 6. Phonocardiograms or auscultograms can be used to record both normal and abnormal sounds using specialized electronic stethoscopes.

During auscultation, it is common practice for the clinician to ask the patient to breathe deeply. This procedure not only allows for listening to airflow, but it may also amplify heart murmurs. Inhalation increases blood flow into the right side of the heart and may increase the amplitude of right-sided heart murmurs. Expiration partially restricts blood flow into the left side of the heart and may amplify left-sided heart murmurs. [\[link\]](#) indicates proper placement of the bell of the stethoscope to facilitate auscultation.

Stethoscope Placement for Auscultation



Proper placement of the bell of the stethoscope facilitates auscultation. At each of the four locations on the chest, a different valve can be heard.

Chapter Review

The cardiac cycle comprises a complete relaxation and contraction of both the atria and ventricles, and lasts approximately 0.8 seconds. Beginning with all chambers in diastole, blood flows passively from the veins into the atria and past the atrioventricular valves into the ventricles. The atria begin to contract (atrial systole), following depolarization of the atria, and pump blood into the ventricles. The ventricles begin to contract (ventricular systole), raising pressure within the ventricles. When ventricular pressure rises above the pressure in the atria, blood flows toward the atria, producing the first heart sound, S_1 or lub. As pressure in the ventricles rises above two major arteries, blood pushes open the two semilunar valves and moves into the pulmonary trunk and aorta in the ventricular ejection phase. Following ventricular repolarization, the ventricles begin to relax (ventricular diastole), and pressure within the ventricles drops. As ventricular pressure drops, there is a tendency for blood to flow back into the atria from the major arteries, producing the dicrotic notch in the ECG and closing the two semilunar valves. The second heart sound, S_2 or dub, occurs when the semilunar valves close. When the pressure falls below that of the atria, blood moves from the atria into the ventricles, opening the atrioventricular valves and marking one complete heart cycle. The valves prevent backflow of blood. Failure of the valves to operate properly produces turbulent blood flow within the heart; the resulting heart murmur can often be heard with a stethoscope.

Review Questions

Exercise:

Problem:

The cardiac cycle consists of a distinct relaxation and contraction phase. Which term is typically used to refer ventricular contraction while no blood is being ejected?

- a. systole
- b. diastole
- c. quiescent
- d. isovolumic contraction

Solution:

D

Exercise:

Problem: Most blood enters the ventricle during _____.

- a. atrial systole
- b. atrial diastole
- c. ventricular systole
- d. isovolumic contraction

Solution:

B

Exercise:**Problem:**

The first heart sound represents which portion of the cardiac cycle?

- a. atrial systole
- b. ventricular systole
- c. closing of the atrioventricular valves

d. closing of the semilunar valves

Solution:

C

Exercise:

Problem: Ventricular relaxation immediately follows _____.

- a. atrial depolarization
- b. ventricular repolarization
- c. ventricular depolarization
- d. atrial repolarization

Solution:

B

Critical Thinking Questions

Exercise:

Problem:

Describe one cardiac cycle, beginning with both atria and ventricles relaxed.

Solution:

The cardiac cycle comprises a complete relaxation and contraction of both the atria and ventricles, and lasts approximately 0.8 seconds. Beginning with all chambers in diastole, blood flows passively from the veins into the atria and past the atrioventricular valves into the ventricles. The atria begin to contract following depolarization of the atria and pump blood into the ventricles. The ventricles begin to

contract, raising pressure within the ventricles. When ventricular pressure rises above the pressure in the two major arteries, blood pushes open the two semilunar valves and moves into the pulmonary trunk and aorta in the ventricular ejection phase. Following ventricular repolarization, the ventricles begin to relax, and pressure within the ventricles drops. When the pressure falls below that of the atria, blood moves from the atria into the ventricles, opening the atrioventricular valves and marking one complete heart cycle.

Glossary

cardiac cycle

period of time between the onset of atrial contraction (atrial systole) and ventricular relaxation (ventricular diastole)

diastole

period of time when the heart muscle is relaxed and the chambers fill with blood

end diastolic volume (EDV)

(also, preload) the amount of blood in the ventricles at the end of atrial systole just prior to ventricular contraction

end systolic volume (ESV)

amount of blood remaining in each ventricle following systole

heart sounds

sounds heard via auscultation with a stethoscope of the closing of the atrioventricular valves (“lub”) and semilunar valves (“dub”)

isovolumic contraction

(also, isovolumetric contraction) initial phase of ventricular contraction in which tension and pressure in the ventricle increase, but no blood is pumped or ejected from the heart

isovolumic ventricular relaxation phase

initial phase of the ventricular diastole when pressure in the ventricles drops below pressure in the two major arteries, the pulmonary trunk, and the aorta, and blood attempts to flow back into the ventricles, producing the aortic notch of the ECG and closing the two semilunar valves

murmur

unusual heart sound detected by auscultation; typically related to septal or valve defects

preload

(also, end diastolic volume) amount of blood in the ventricles at the end of atrial systole just prior to ventricular contraction

systole

period of time when the heart muscle is contracting

ventricular ejection phase

second phase of ventricular systole during which blood is pumped from the ventricle

Cardiac Physiology

By the end of this section, you will be able to:

- Relate heart rate to cardiac output
- Describe the effect of exercise on heart rate
- Identify cardiovascular centers and cardiac reflexes that regulate heart function
- Describe factors affecting heart rate
- Distinguish between positive and negative factors that affect heart contractility
- Summarize factors affecting stroke volume and cardiac output
- Describe the cardiac response to variations in blood flow and pressure

The autorhythmicity inherent in cardiac cells keeps the heart beating at a regular pace; however, the heart is regulated by and responds to outside influences as well. Neural and endocrine controls are vital to the regulation of cardiac function. In addition, the heart is sensitive to several environmental factors, including electrolytes.

Resting Cardiac Output

Cardiac output (CO) is a measurement of the amount of blood pumped by each ventricle in one minute. To calculate this value, multiply **stroke volume (SV)**, the amount of blood pumped by each ventricle, by **heart rate (HR)**, in contractions per minute (or beats per minute, bpm). It can be represented mathematically by the following equation:

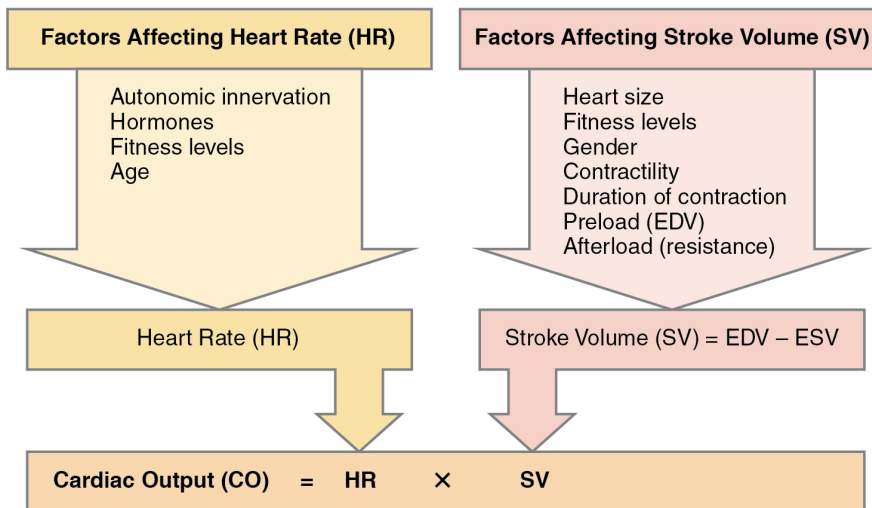
$$CO = HR \times SV$$

SV is normally measured using an echocardiogram to record EDV and ESV, and calculating the difference: $SV = EDV - ESV$. SV can also be measured using a specialized catheter, but this is an invasive procedure and far more dangerous to the patient. A mean SV for a resting 70-kg (150-lb) individual would be approximately 70 mL. There are several important variables, including size of the heart, physical and mental condition of the individual, sex, contractility, duration of contraction, preload or EDV, and afterload or resistance. Normal range for SV would be 55–100 mL. An average resting

HR would be approximately 75 bpm but could range from 60–100 in some individuals.

Using these numbers, the mean CO is 5.25 L/min, with a range of 4.0–8.0 L/min. Remember, however, that these numbers refer to CO from each ventricle separately, not the total for the heart. Factors influencing CO are summarized in [\[link\]](#).

Major Factors Influencing Cardiac Output



Cardiac output is influenced by heart rate and stroke volume, both of which are also variable.

SVs are also used to calculate **ejection fraction**, which is the portion of the blood that is pumped or ejected from the heart with each contraction. To calculate ejection fraction, SV is divided by EDV. Despite the name, the ejection fraction is normally expressed as a percentage. Ejection fractions range from approximately 55–70 percent, with a mean of 58 percent.

Exercise and Maximum Cardiac Output

In healthy young individuals, HR may increase to 150 bpm during exercise. SV can also increase from 70 to approximately 130 mL due to increased strength of contraction. This would increase CO to approximately 19.5

L/min, 4–5 times the resting rate. Top cardiovascular athletes can achieve even higher levels. At their peak performance, they may increase resting CO by 7–8 times.

Since the heart is a muscle, exercising it increases its efficiency. The difference between maximum and resting CO is known as the **cardiac reserve**. It measures the residual capacity of the heart to pump blood.

Heart Rates

HRs vary considerably, not only with exercise and fitness levels, but also with age. Newborn resting HRs may be 120 bpm. HR gradually decreases until young adulthood and then gradually increases again with age.

Maximum HRs are normally in the range of 200–220 bpm, although there are some extreme cases in which they may reach higher levels. As one ages, the ability to generate maximum rates decreases. This may be estimated by taking the maximal value of 220 bpm and subtracting the individual's age. So a 40-year-old individual would be expected to hit a maximum rate of approximately 180, and a 60-year-old person would achieve a HR of 160.

Note:

Disorders of the...

Heart: Abnormal Heart Rates

For an adult, normal resting HR will be in the range of 60–100 bpm.

Bradycardia is the condition in which resting rate drops below 60 bpm, and tachycardia is the condition in which the resting rate is above 100 bpm.

Trained athletes typically have very low HRs. If the patient is not exhibiting other symptoms, such as weakness, fatigue, dizziness, fainting, chest discomfort, palpitations, or respiratory distress, bradycardia is not considered clinically significant. However, if any of these symptoms are present, they may indicate that the heart is not providing sufficient oxygenated blood to the tissues. The term relative bradycardia may be used with a patient who has a HR in the normal range but is still suffering from

these symptoms. Most patients remain asymptomatic as long as the HR remains above 50 bpm.

Bradycardia may be caused by either inherent factors or causes external to the heart. While the condition may be inherited, typically it is acquired in older individuals. Inherent causes include abnormalities in either the SA or AV node. If the condition is serious, a pacemaker may be required. Other causes include ischemia to the heart muscle or diseases of the heart vessels or valves. External causes include metabolic disorders, pathologies of the endocrine system often involving the thyroid, electrolyte imbalances, neurological disorders including inappropriate autonomic responses, autoimmune pathologies, over-prescription of beta blocker drugs that reduce HR, recreational drug use, or even prolonged bed rest. Treatment relies upon establishing the underlying cause of the disorder and may necessitate supplemental oxygen.

Tachycardia is not normal in a resting patient but may be detected in pregnant women or individuals experiencing extreme stress. In the latter case, it would likely be triggered by stimulation from the limbic system or disorders of the autonomic nervous system. In some cases, tachycardia may involve only the atria. Some individuals may remain asymptomatic, but when present, symptoms may include dizziness, shortness of breath, lightheadedness, rapid pulse, heart palpitations, chest pain, or fainting (syncope). While tachycardia is defined as a HR above 100 bpm, there is considerable variation among people. Further, the normal resting HRs of children are often above 100 bpm, but this is not considered to be tachycardia. Many causes of tachycardia may be benign, but the condition may also be correlated with fever, anemia, hypoxia, hyperthyroidism, hypersecretion of catecholamines, some cardiomyopathies, some disorders of the valves, and acute exposure to radiation. Elevated rates in an exercising or resting patient are normal and expected. Resting rate should always be taken after recovery from exercise. Treatment depends upon the underlying cause but may include medications, implantable cardioverter defibrillators, ablation, or surgery.

Correlation Between Heart Rates and Cardiac Output

Initially, physiological conditions that cause HR to increase also trigger an increase in SV. During exercise, the rate of blood returning to the heart increases. However as the HR rises, there is less time spent in diastole and consequently less time for the ventricles to fill with blood. Even though there is less filling time, SV will initially remain high. However, as HR continues to increase, SV gradually decreases due to decreased filling time. CO will initially stabilize as the increasing HR compensates for the decreasing SV, but at very high rates, CO will eventually decrease as increasing rates are no longer able to compensate for the decreasing SV. Consider this phenomenon in a healthy young individual. Initially, as HR increases from resting to approximately 120 bpm, CO will rise. As HR increases from 120 to 160 bpm, CO remains stable, since the increase in rate is offset by decreasing ventricular filling time and, consequently, SV. As HR continues to rise above 160 bpm, CO actually decreases as SV falls faster than HR increases. So although aerobic exercises are critical to maintain the health of the heart, individuals are cautioned to monitor their HR to ensure they stay within the **target heart rate** range of between 120 and 160 bpm, so CO is maintained. The target HR is loosely defined as the range in which both the heart and lungs receive the maximum benefit from the aerobic workout and is dependent upon age.

Cardiovascular Centers

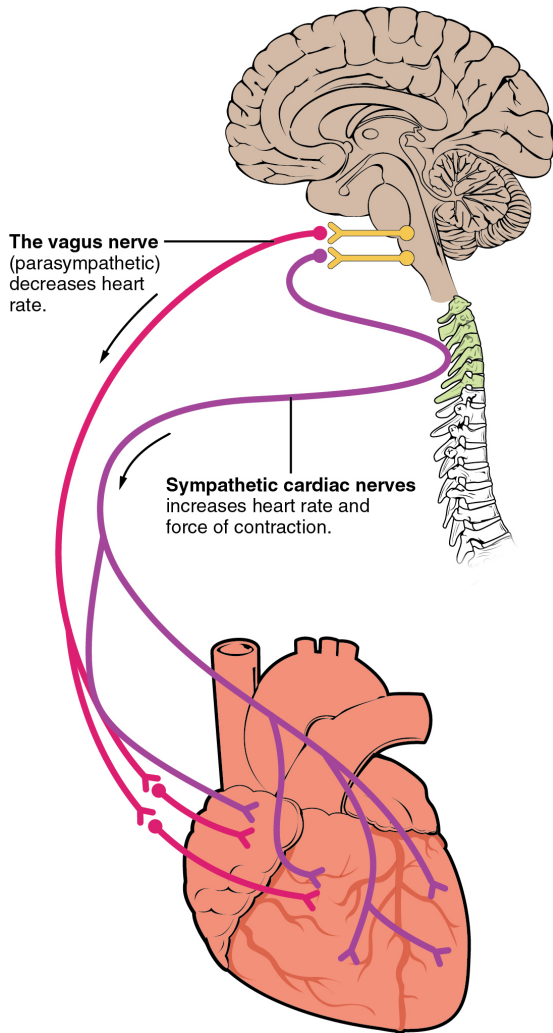
Nervous control over HR is centralized within the two paired cardiovascular centers of the medulla oblongata ([\[link\]](#)). The cardioaccelerator regions stimulate activity via sympathetic stimulation of the cardioaccelerator nerves, and the cardioinhibitory centers decrease heart activity via parasympathetic stimulation as one component of the vagus nerve, cranial nerve X. During rest, both centers provide slight stimulation to the heart, contributing to **autonomic tone**. This is a similar concept to tone in skeletal muscles. Normally, vagal stimulation predominates as, left unregulated, the SA node would initiate a sinus rhythm of approximately 100 bpm.

Both sympathetic and parasympathetic stimulations flow through a paired complex network of nerve fibers known as the **cardiac plexus** near the base of the heart. The cardioaccelerator center also sends additional fibers,

forming the cardiac nerves via sympathetic ganglia (the cervical ganglia plus superior thoracic ganglia T1–T4) to both the SA and AV nodes, plus additional fibers to the atria and ventricles. The ventricles are more richly innervated by sympathetic fibers than parasympathetic fibers. Sympathetic stimulation causes the release of the neurotransmitter norepinephrine (NE) at the neuromuscular junction of the cardiac nerves. NE shortens the repolarization period, thus speeding the rate of depolarization and contraction, which results in an increase in HR. It opens chemical- or ligand-gated sodium and calcium ion channels, allowing an influx of positively charged ions.

NE binds to the beta-1 receptor. Some cardiac medications (for example, beta blockers) work by blocking these receptors, thereby slowing HR and are one possible treatment for hypertension. Overprescription of these drugs may lead to bradycardia and even stoppage of the heart.

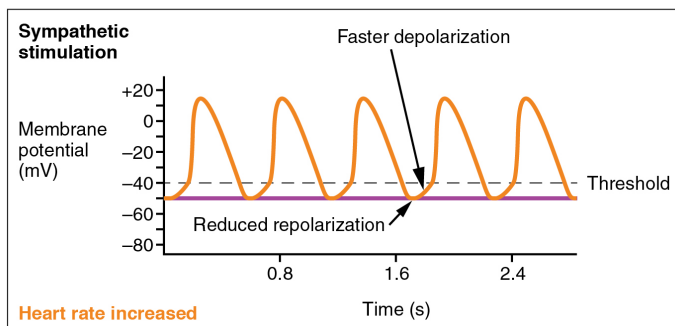
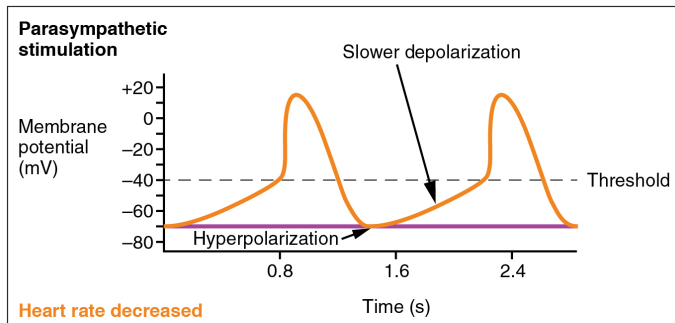
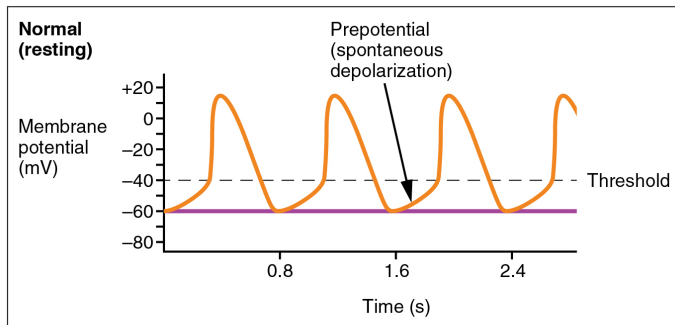
Autonomic Innervation of the Heart



Cardioaccelerator and cardioinhibitory areas are components of the paired cardiac centers located in the medulla oblongata of the brain. They innervate the heart via sympathetic cardiac nerves that increase cardiac activity and vagus (parasympathetic) nerves that slow cardiac activity.

Parasympathetic stimulation originates from the cardioinhibitory region with impulses traveling via the vagus nerve (cranial nerve X). The vagus nerve sends branches to both the SA and AV nodes, and to portions of both the atria and ventricles. Parasympathetic stimulation releases the neurotransmitter acetylcholine (ACh) at the neuromuscular junction. ACh slows HR by opening chemical- or ligand-gated potassium ion channels to slow the rate of spontaneous depolarization, which extends repolarization and increases the time before the next spontaneous depolarization occurs. Without any nervous stimulation, the SA node would establish a sinus rhythm of approximately 100 bpm. Since resting rates are considerably less than this, it becomes evident that parasympathetic stimulation normally slows HR. This is similar to an individual driving a car with one foot on the brake pedal. To speed up, one need merely remove one's foot from the break and let the engine increase speed. In the case of the heart, decreasing parasympathetic stimulation decreases the release of ACh, which allows HR to increase up to approximately 100 bpm. Any increases beyond this rate would require sympathetic stimulation. [\[link\]](#) illustrates the effects of parasympathetic and sympathetic stimulation on the normal sinus rhythm.

Effects of Parasympathetic and Sympathetic Stimulation on Normal Sinus Rhythm



The wave of depolarization in a normal sinus rhythm shows a stable resting HR. Following parasympathetic stimulation, HR slows. Following sympathetic stimulation, HR increases.

Input to the Cardiovascular Center

The cardiovascular center receives input from a series of visceral receptors with impulses traveling through visceral sensory fibers within the vagus and

sympathetic nerves via the cardiac plexus. Among these receptors are various proprioceptors, baroreceptors, and chemoreceptors, plus stimuli from the limbic system. Collectively, these inputs normally enable the cardiovascular centers to regulate heart function precisely, a process known as **cardiac reflexes**. Increased physical activity results in increased rates of firing by various proprioceptors located in muscles, joint capsules, and tendons. Any such increase in physical activity would logically warrant increased blood flow. The cardiac centers monitor these increased rates of firing, and suppress parasympathetic stimulation and increase sympathetic stimulation as needed in order to increase blood flow.

Similarly, baroreceptors are stretch receptors located in the aortic sinus, carotid bodies, the venae cavae, and other locations, including pulmonary vessels and the right side of the heart itself. Rates of firing from the baroreceptors represent blood pressure, level of physical activity, and the relative distribution of blood. The cardiac centers monitor baroreceptor firing to maintain cardiac homeostasis, a mechanism called the **baroreceptor reflex**. With increased pressure and stretch, the rate of baroreceptor firing increases, and the cardiac centers decrease sympathetic stimulation and increase parasympathetic stimulation. As pressure and stretch decrease, the rate of baroreceptor firing decreases, and the cardiac centers increase sympathetic stimulation and decrease parasympathetic stimulation.

There is a similar reflex, called the **atrial reflex** or **Bainbridge reflex**, associated with varying rates of blood flow to the atria. Increased venous return stretches the walls of the atria where specialized baroreceptors are located. However, as the atrial baroreceptors increase their rate of firing and as they stretch due to the increased blood pressure, the cardiac center responds by increasing sympathetic stimulation and inhibiting parasympathetic stimulation to increase HR. The opposite is also true.

Increased metabolic byproducts associated with increased activity, such as carbon dioxide, hydrogen ions, and lactic acid, plus falling oxygen levels, are detected by a suite of chemoreceptors innervated by the glossopharyngeal and vagus nerves. These chemoreceptors provide

feedback to the cardiovascular centers about the need for increased or decreased blood flow, based on the relative levels of these substances.

The limbic system can also significantly impact HR related to emotional state. During periods of stress, it is not unusual to identify higher than normal HRs, often accompanied by a surge in the stress hormone cortisol. Individuals experiencing extreme anxiety may manifest panic attacks with symptoms that resemble those of heart attacks. These events are typically transient and treatable. Meditation techniques have been developed to ease anxiety and have been shown to lower HR effectively. Doing simple deep and slow breathing exercises with one's eyes closed can also significantly reduce this anxiety and HR.

Note:

Disorders of the...

Heart: Broken Heart Syndrome

Extreme stress from such life events as the death of a loved one, an emotional break up, loss of income, or foreclosure of a home may lead to a condition commonly referred to as broken heart syndrome. This condition may also be called Takotsubo cardiomyopathy, transient apical ballooning syndrome, apical ballooning cardiomyopathy, stress-induced cardiomyopathy, Gebrochenes-Herz syndrome, and stress cardiomyopathy. The recognized effects on the heart include congestive heart failure due to a profound weakening of the myocardium not related to lack of oxygen. This may lead to acute heart failure, lethal arrhythmias, or even the rupture of a ventricle. The exact etiology is not known, but several factors have been suggested, including transient vasospasm, dysfunction of the cardiac capillaries, or thickening of the myocardium—particularly in the left ventricle—that may lead to the critical circulation of blood to this region. While many patients survive the initial acute event with treatment to restore normal function, there is a strong correlation with death. Careful statistical analysis by the Cass Business School, a prestigious institution located in London, published in 2008, revealed that within one year of the death of a loved one, women are more than twice as likely to die and males are six times as likely to die as would otherwise be expected.

Other Factors Influencing Heart Rate

Using a combination of autorhythmicity and innervation, the cardiovascular center is able to provide relatively precise control over HR. However, there are a number of other factors that have an impact on HR as well, including epinephrine, NE, and thyroid hormones; levels of various ions including calcium, potassium, and sodium; body temperature; hypoxia; and pH balance ([\[link\]](#) and [\[link\]](#)). After reading this section, the importance of maintaining homeostasis should become even more apparent.

| Major Factors Increasing Heart Rate and Force of Contraction | |
|--|---|
| Factor | Effect |
| Cardioaccelerator nerves | Release of norepinephrine by cardioaccelerator nerves |
| Proprioreceptors | Increased firing rates of proprioreceptors (e.g. during exercise) |
| Chemoreceptors | Chemoreceptors sensing decreased levels of O ₂ or increased levels of H ⁺ , CO ₂ and lactic acid |
| Baroreceptors | Decreased firing rates of baroreceptors (indicating falling blood volume/pressure) |
| Limbic system | Anticipation of physical exercise or strong emotions by the limbic system |
| Catecholamines | Increased epinephrine and norepinephrine release by the adrenal glands |

| Major Factors Increasing Heart Rate and Force of Contraction | |
|---|--|
| Factor | Effect |
| Thyroid hormones | Increased T_3 and T_4 in the blood (released by thyroid) |
| Calcium | Increase in calcium ions in the blood |
| Potassium | Decrease in potassium ions in the blood |
| Sodium | Decrease in sodium ions in the blood |
| Body temperature | Increase in body temperature |
| Nicotine and caffeine | Presence of nicotine, caffeine or other stimulants |

| Factors Decreasing Heart Rate and Force of Contraction | |
|---|--|
| Factor | Effect |
| Cardioinhibitor nerves (vagus) | Release of acetylcholine by cardioaccelerator nerves |
| Proprioreceptors | Decreased firing rates of proprioreceptors (e.g. during rest) |
| Chemoreceptors | Chemoreceptors sensing increased levels of O_2 or decreased levels of H^+ , CO_2 and lactic acid |

| Factors Decreasing Heart Rate and Force of Contraction | |
|---|---|
| Factor | Effect |
| Baroreceptors | Increased firing rates of baroreceptors (indicating rising blood volume/pressure) |
| Limbic system | Anticipation of relaxation by the limbic system |
| Catecholamines | Increased epinephrine and norepinephrine release by the adrenal glands |
| Thyroid hormones | Decreased T ₃ and T ₄ in the blood (released by thyroid) |
| Calcium | Increase in calcium ions in the blood |
| Potassium | Increase in potassium ions in the blood |
| Sodium | Increase in sodium ions in the blood |
| Body temperature | Decrease in body temperature |
| Opiates and tranquilizers | Presence of opiates (heroin), tranquilizers or other depressants |

Epinephrine and Norepinephrine

The catecholamines, epinephrine and NE, secreted by the adrenal medulla form one component of the extended fight-or-flight mechanism. The other component is sympathetic stimulation. Epinephrine and NE have similar effects: binding to the beta-1 receptors, and opening sodium and calcium ion chemical- or ligand-gated channels. The rate of depolarization is increased by this additional influx of positively charged ions, so the

threshold is reached more quickly and the period of repolarization is shortened. However, massive releases of these hormones coupled with sympathetic stimulation may actually lead to arrhythmias. There is no parasympathetic stimulation to the adrenal medulla.

Thyroid Hormones

In general, increased levels of thyroid hormone, or thyroxin, increase cardiac rate and contractility. The impact of thyroid hormone is typically of a much longer duration than that of the catecholamines. The physiologically active form of thyroid hormone, T_3 or triiodothyronine, has been shown to directly enter cardiomyocytes and alter activity at the level of the genome. It also impacts the beta adrenergic response similar to epinephrine and NE described above. Excessive levels of thyroxin may trigger tachycardia.

Calcium

Calcium ion levels have great impacts upon both HR and contractility; as the levels of calcium ions increase, so do HR and contractility. High levels of calcium ions (hypercalcemia) may be implicated in a short QT interval and a widened T wave in the ECG. The QT interval represents the time from the start of depolarization to repolarization of the ventricles, and includes the period of ventricular systole. Extremely high levels of calcium may induce cardiac arrest. Drugs known as calcium channel blockers slow HR by binding to these channels and blocking or slowing the inward movement of calcium ions.

Caffeine and Nicotine

Caffeine and nicotine are not found naturally within the body. Both of these nonregulated drugs have an excitatory effect on membranes of neurons in general and have a stimulatory effect on the cardiac centers specifically, causing an increase in HR. Caffeine works by increasing the rates of

depolarization at the SA node, whereas nicotine stimulates the activity of the sympathetic neurons that deliver impulses to the heart.

Although it is the world's most widely consumed psychoactive drug, caffeine is legal and not regulated. While precise quantities have not been established, "normal" consumption is not considered harmful to most people, although it may cause disruptions to sleep and acts as a diuretic. Its consumption by pregnant women is cautioned against, although no evidence of negative effects has been confirmed. Tolerance and even physical and mental addiction to the drug result in individuals who routinely consume the substance.

Nicotine, too, is a stimulant and produces addiction. While legal and nonregulated, concerns about nicotine's safety and documented links to respiratory and cardiac disease have resulted in warning labels on cigarette packages.

Factors Decreasing Heart Rate

HR can be slowed when a person experiences altered sodium and potassium levels, hypoxia, acidosis, alkalosis, and hypothermia (see [\[link\]](#)). The relationship between electrolytes and HR is complex, but maintaining electrolyte balance is critical to the normal wave of depolarization. Of the two ions, potassium has the greater clinical significance. Initially, both hyponatremia (low sodium levels) and hypernatremia (high sodium levels) may lead to tachycardia. Severely high hypernatremia may lead to fibrillation, which may cause CO to cease. Severe hyponatremia leads to both bradycardia and other arrhythmias. Hypokalemia (low potassium levels) also leads to arrhythmias, whereas hyperkalemia (high potassium levels) causes the heart to become weak and flaccid, and ultimately to fail.

Acidosis is a condition in which excess hydrogen ions are present, and the patient's blood expresses a low pH value. Alkalosis is a condition in which there are too few hydrogen ions, and the patient's blood has an elevated pH. Normal blood pH falls in the range of 7.35–7.45, so a number lower than this range represents acidosis and a higher number represents alkalosis.

Recall that enzymes are the regulators or catalysts of virtually all biochemical reactions; they are sensitive to pH and will change shape slightly with values outside their normal range. These variations in pH and accompanying slight physical changes to the active site on the enzyme decrease the rate of formation of the enzyme-substrate complex, subsequently decreasing the rate of many enzymatic reactions, which can have complex effects on HR. Severe changes in pH will lead to denaturation of the enzyme.

The last variable is body temperature. Elevated body temperature is called hyperthermia, and suppressed body temperature is called hypothermia. Slight hyperthermia results in increasing HR and strength of contraction. Hypothermia slows the rate and strength of heart contractions. This distinct slowing of the heart is one component of the larger diving reflex that diverts blood to essential organs while submerged. If sufficiently chilled, the heart will stop beating, a technique that may be employed during open heart surgery. In this case, the patient's blood is normally diverted to an artificial heart-lung machine to maintain the body's blood supply and gas exchange until the surgery is complete, and sinus rhythm can be restored. Excessive hyperthermia and hypothermia will both result in death, as enzymes drive the body systems to cease normal function, beginning with the central nervous system.

Stroke Volume

Many of the same factors that regulate HR also impact cardiac function by altering SV. While a number of variables are involved, SV is ultimately dependent upon the difference between EDV and ESV. The three primary factors to consider are preload, or the stretch on the ventricles prior to contraction; the contractility, or the force or strength of the contraction itself; and afterload, the force the ventricles must generate to pump blood against the resistance in the vessels. These factors are summarized in [\[link\]](#) and [\[link\]](#).

Preload

Preload is another way of expressing EDV. Therefore, the greater the EDV is, the greater the preload is. One of the primary factors to consider is **filling time**, or the duration of ventricular diastole during which filling occurs. The more rapidly the heart contracts, the shorter the filling time becomes, and the lower the EDV and preload are. This effect can be partially overcome by increasing the second variable, contractility, and raising SV, but over time, the heart is unable to compensate for decreased filling time, and preload also decreases.

With increasing ventricular filling, both EDV or preload increase, and the cardiac muscle itself is stretched to a greater degree. At rest, there is little stretch of the ventricular muscle, and the sarcomeres remain short. With increased ventricular filling, the ventricular muscle is increasingly stretched and the sarcomere length increases. As the sarcomeres reach their optimal lengths, they will contract more powerfully, because more of the myosin heads can bind to the actin on the thin filaments, forming cross bridges and increasing the strength of contraction and SV. If this process were to continue and the sarcomeres stretched beyond their optimal lengths, the force of contraction would decrease. However, due to the physical constraints of the location of the heart, this excessive stretch is not a concern.

The relationship between ventricular stretch and contraction has been stated in the well-known **Frank-Starling mechanism** or simply Starling's Law of the Heart. This principle states that, within physiological limits, the force of heart contraction is directly proportional to the initial length of the muscle fiber. This means that the greater the stretch of the ventricular muscle (within limits), the more powerful the contraction is, which in turn increases SV. Therefore, by increasing preload, you increase the second variable, contractility.

Otto Frank (1865–1944) was a German physiologist; among his many published works are detailed studies of this important heart relationship. Ernest Starling (1866–1927) was an important English physiologist who also studied the heart. Although they worked largely independently, their combined efforts and similar conclusions have been recognized in the name “Frank-Starling mechanism.”

Any sympathetic stimulation to the venous system will increase venous return to the heart, which contributes to ventricular filling, and EDV and preload. While much of the ventricular filling occurs while both atria and ventricles are in diastole, the contraction of the atria, the atrial kick, plays a crucial role by providing the last 20–30 percent of ventricular filling.

Contractility

It is virtually impossible to consider preload or ESV without including an early mention of the concept of contractility. Indeed, the two parameters are intimately linked. Contractility refers to the force of the contraction of the heart muscle, which controls SV, and is the primary parameter for impacting ESV. The more forceful the contraction is, the greater the SV and smaller the ESV are. Less forceful contractions result in smaller SVs and larger ESVs. Factors that increase contractility are described as **positive inotropic factors**, and those that decrease contractility are described as **negative inotropic factors** (ino- = “fiber;” -tropic = “turning toward”).

Not surprisingly, sympathetic stimulation is a positive inotrope, whereas parasympathetic stimulation is a negative inotrope. Sympathetic stimulation triggers the release of NE at the neuromuscular junction from the cardiac nerves and also stimulates the adrenal cortex to secrete epinephrine and NE. In addition to their stimulatory effects on HR, they also bind to both alpha and beta receptors on the cardiac muscle cell membrane to increase metabolic rate and the force of contraction. This combination of actions has the net effect of increasing SV and leaving a smaller residual ESV in the ventricles. In comparison, parasympathetic stimulation releases ACh at the neuromuscular junction from the vagus nerve. The membrane hyperpolarizes and inhibits contraction to decrease the strength of contraction and SV, and to raise ESV. Since parasympathetic fibers are more widespread in the atria than in the ventricles, the primary site of action is in the upper chambers. Parasympathetic stimulation in the atria decreases the atrial kick and reduces EDV, which decreases ventricular stretch and preload, thereby further limiting the force of ventricular contraction. Stronger parasympathetic stimulation also directly decreases the force of contraction of the ventricles.

Several synthetic drugs, including dopamine and isoproterenol, have been developed that mimic the effects of epinephrine and NE by stimulating the influx of calcium ions from the extracellular fluid. Higher concentrations of intracellular calcium ions increase the strength of contraction. Excess calcium (hypercalcemia) also acts as a positive inotropic agent. The drug digitalis lowers HR and increases the strength of the contraction, acting as a positive inotropic agent by blocking the sequestering of calcium ions into the sarcoplasmic reticulum. This leads to higher intracellular calcium levels and greater strength of contraction. In addition to the catecholamines from the adrenal medulla, other hormones also demonstrate positive inotropic effects. These include thyroid hormones and glucagon from the pancreas.

Negative inotropic agents include hypoxia, acidosis, hyperkalemia, and a variety of synthetic drugs. These include numerous beta blockers and calcium channel blockers. Early beta blocker drugs include propranolol and pronethalol, and are credited with revolutionizing treatment of cardiac patients experiencing angina pectoris. There is also a large class of dihydropyridine, phenylalkylamine, and benzothiazepine calcium channel blockers that may be administered decreasing the strength of contraction and SV.

Afterload

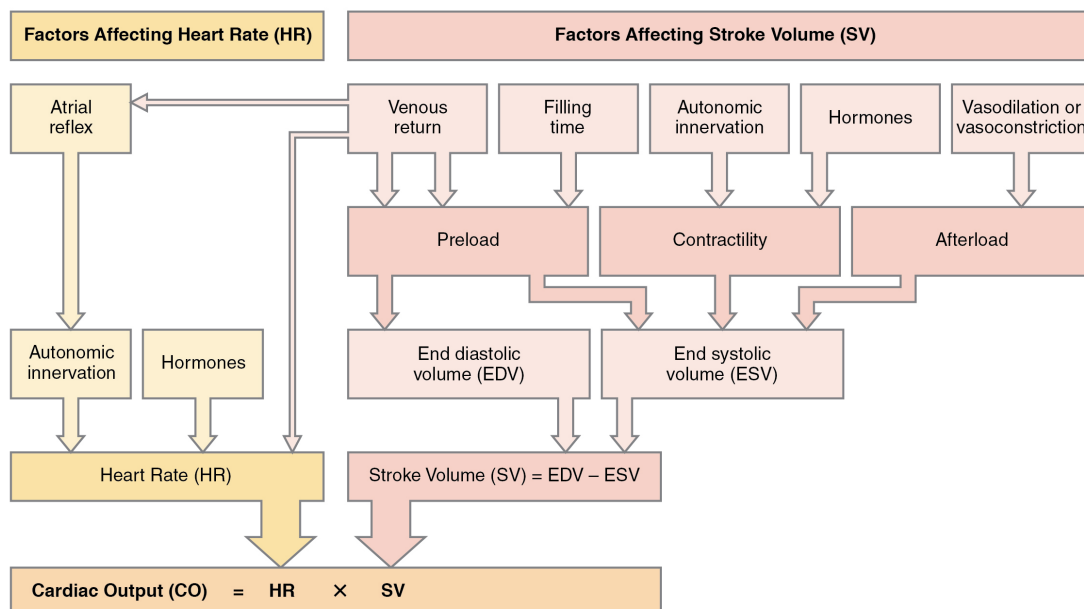
Afterload refers to the tension that the ventricles must develop to pump blood effectively against the resistance in the vascular system. Any condition that increases resistance requires a greater afterload to force open the semilunar valves and pump the blood. Damage to the valves, such as stenosis, which makes them harder to open will also increase afterload. Any decrease in resistance decreases the afterload. [\[link\]](#) summarizes the major factors influencing SV, [\[link\]](#) summarizes the major factors influencing CO, and [\[link\]](#) and [\[link\]](#) summarize cardiac responses to increased and decreased blood flow and pressure in order to restore homeostasis.

Major Factors Influencing Stroke Volume

| Factors Affecting Stroke Volume (SV) | | | |
|--------------------------------------|--|---|---|
| | Preload | Contractility | Afterload |
| Raised due to: | <ul style="list-style-type: none"> • fast filling time • increased venous return <p>Increases end diastolic volume, Increases stroke volume</p> | <ul style="list-style-type: none"> • sympathetic stimulation • epinephrine and norepinephrine • high intracellular calcium ions • high blood calcium level • thyroid hormones • glucagon <p>Decreases end systolic volume, Increases stroke volume</p> | <ul style="list-style-type: none"> • increased vascular resistance • semilunar valve damage <p>Increases end systolic volume Decreases stroke volume</p> |
| Lowered due to: | <ul style="list-style-type: none"> • decreased thyroid hormones • decreased calcium ions • high or low potassium ions • high or low sodium • low body temperature • hypoxia • abnormal pH balance • drugs (i.e., calcium channel blockers) <p>Decreases end diastolic volume, Decreases stroke volume</p> | <ul style="list-style-type: none"> • parasympathetic stimulation • acetylcholine • hypoxia • hyperkalemia <p>Increases end systolic volume Decreases stroke volume</p> | <ul style="list-style-type: none"> • decreased vascular resistance <p>Decreases end systolic volume Increases stroke volume</p> |

Multiple factors impact preload, afterload, and contractility, and are the major considerations influencing SV.

Summary of Major Factors Influencing Cardiac Output



The primary factors influencing HR include autonomic innervation plus endocrine control. Not shown are environmental factors, such as electrolytes, metabolic products,

and temperature. The primary factors controlling SV include preload, contractility, and afterload. Other factors such as electrolytes may be classified as either positive or negative inotropic agents.

| Cardiac Response to Decreasing Blood Flow and Pressure Due to Decreasing Cardiac Output | | |
|--|--|---|
| | Baroreceptors (aorta, carotid arteries, venae cavae, and atria) | Chemoreceptors (both central nervous system and in proximity to baroreceptors) |
| Sensitive to | Decreasing stretch | Decreasing O ₂ and increasing CO ₂ , H ⁺ , and lactic acid |
| Target | Parasympathetic stimulation suppressed | Sympathetic stimulation increased |
| Response of heart | Increasing heart rate and increasing stroke volume | Increasing heart rate and increasing stroke volume |
| Overall effect | Increasing blood flow and pressure due to increasing cardiac output; hemostasis restored | Increasing blood flow and pressure due to increasing cardiac output; hemostasis restored |

| Cardiac Response to Increasing Blood Flow and Pressure Due to Increasing Cardiac Output | | |
|--|--|---|
| | Baroreceptors (aorta, carotid arteries, venae cavae, and atria) | Chemoreceptors (both central nervous system and in proximity to baroreceptors) |
| Sensitive to | Increasing stretch | Increasing O ₂ and decreasing CO ₂ , H ⁺ , and lactic acid |
| Target | Parasympathetic stimulation increased | Sympathetic stimulation suppressed |
| Response of heart | Decreasing heart rate and decreasing stroke volume | Decreasing heart rate and decreasing stroke volume |
| Overall effect | Decreasing blood flow and pressure due to decreasing cardiac output; hemostasis restored | Decreasing blood flow and pressure due to decreasing cardiac output; hemostasis restored |

Chapter Review

Many factors affect HR and SV, and together, they contribute to cardiac function. HR is largely determined and regulated by autonomic stimulation and hormones. There are several feedback loops that contribute to maintaining homeostasis dependent upon activity levels, such as the atrial reflex, which is determined by venous return.

SV is regulated by autonomic innervation and hormones, but also by filling time and venous return. Venous return is determined by activity of the skeletal muscles, blood volume, and changes in peripheral circulation.

Venous return determines preload and the atrial reflex. Filling time directly related to HR also determines preload. Preload then impacts both EDV and ESV. Autonomic innervation and hormones largely regulate contractility. Contractility impacts EDV as does afterload. CO is the product of HR multiplied by SV. SV is the difference between EDV and ESV.

Review Questions

Exercise:

Problem:

The force the heart must overcome to pump blood is known as _____.

- a. preload
- b. afterload
- c. cardiac output
- d. stroke volume

Solution:

B

Exercise:

Problem:

The cardiovascular centers are located in which area of the brain?

- a. medulla oblongata
- b. pons
- c. mesencephalon (midbrain)
- d. cerebrum

Solution:

A

Exercise:

Problem:

In a healthy young adult, what happens to cardiac output when heart rate increases above 160 bpm?

- a. It increases.
 - b. It decreases.
 - c. It remains constant.
 - d. There is no way to predict.
-

Solution:

B

Exercise:

Problem:

What happens to preload when there is venous constriction in the veins?

- a. It increases.
 - b. It decreases.
 - c. It remains constant.
 - d. There is no way to predict.
-

Solution:

A

Exercise:

Problem: Which of the following is a positive inotrope?

- a. Na^+

- b. K^+
- c. Ca^{2+}
- d. both Na^+ and K^+

Solution:

C

Critical Thinking Questions

Exercise:

Problem: Why does increasing EDV increase contractility?

Solution:

Increasing EDV increases the sarcomeres' lengths within the cardiac muscle cells, allowing more cross bridge formation between the myosin and actin and providing for a more powerful contraction. This relationship is described in the Frank-Starling mechanism.

Exercise:

Problem: Why is afterload important to cardiac function?

Solution:

Afterload represents the resistance within the arteries to the flow of blood ejected from the ventricles. If uncompensated, if afterload increases, flow will decrease. In order for the heart to maintain adequate flow to overcome increasing afterload, it must pump more forcefully. This is one of the negative consequences of high blood pressure or hypertension.

Glossary

afterload

force the ventricles must develop to effectively pump blood against the resistance in the vessels

autonomic tone

contractile state during resting cardiac activity produced by mild sympathetic and parasympathetic stimulation

atrial reflex

(also, called Bainbridge reflex) autonomic reflex that responds to stretch receptors in the atria that send impulses to the cardioaccelerator area to increase HR when venous flow into the atria increases

Bainbridge reflex

(also, called atrial reflex) autonomic reflex that responds to stretch receptors in the atria that send impulses to the cardioaccelerator area to increase HR when venous flow into the atria increases

baroreceptor reflex

autonomic reflex in which the cardiac centers monitor signals from the baroreceptor stretch receptors and regulate heart function based on blood flow

cardiac output (CO)

amount of blood pumped by each ventricle during one minute; equals HR multiplied by SV

cardiac plexus

paired complex network of nerve fibers near the base of the heart that receive sympathetic and parasympathetic stimulations to regulate HR

cardiac reflexes

series of autonomic reflexes that enable the cardiovascular centers to regulate heart function based upon sensory information from a variety of visceral sensors

cardiac reserve

difference between maximum and resting CO

ejection fraction

portion of the blood that is pumped or ejected from the heart with each contraction; mathematically represented by SV divided by EDV

filling time

duration of ventricular diastole during which filling occurs

Frank-Starling mechanism

relationship between ventricular stretch and contraction in which the force of heart contraction is directly proportional to the initial length of the muscle fiber

heart rate (HR)

number of times the heart contracts (beats) per minute

negative inotropic factors

factors that negatively impact or lower heart contractility

positive inotropic factors

factors that positively impact or increase heart contractility

stroke volume (SV)

amount of blood pumped by each ventricle per contraction; also, the difference between EDV and ESV

target heart rate

range in which both the heart and lungs receive the maximum benefit from an aerobic workout

Introduction

class="introduction"

Blood Vessels

While most blood vessels are located deep from the surface and are not visible, the superficial veins of the upper limb provide an indication of the extent, prominence, and importance of these structures to the body.
(credit: Colin Davis)

**Note:****Chapter Objectives**

After studying this chapter, you will be able to:

- Compare and contrast the anatomical structure of arteries, arterioles, capillaries, venules, and veins
- Accurately describe the forces that account for capillary exchange
- List the major factors affecting blood flow, blood pressure, and resistance
- Describe how blood flow, blood pressure, and resistance interrelate
- Discuss how the neural and endocrine mechanisms maintain homeostasis within the blood vessels
- Describe the interaction of the cardiovascular system with other body systems
- Label the major blood vessels of the pulmonary and systemic circulations
- Identify and describe the hepatic portal system

- Describe the development of blood vessels and fetal circulation
- Compare fetal circulation to that of an individual after birth

In this chapter, you will learn about the vascular part of the cardiovascular system, that is, the vessels that transport blood throughout the body and provide the physical site where gases, nutrients, and other substances are exchanged with body cells. When vessel functioning is reduced, blood-borne substances do not circulate effectively throughout the body. As a result, tissue injury occurs, metabolism is impaired, and the functions of every bodily system are threatened.

Structure and Function of Blood Vessels

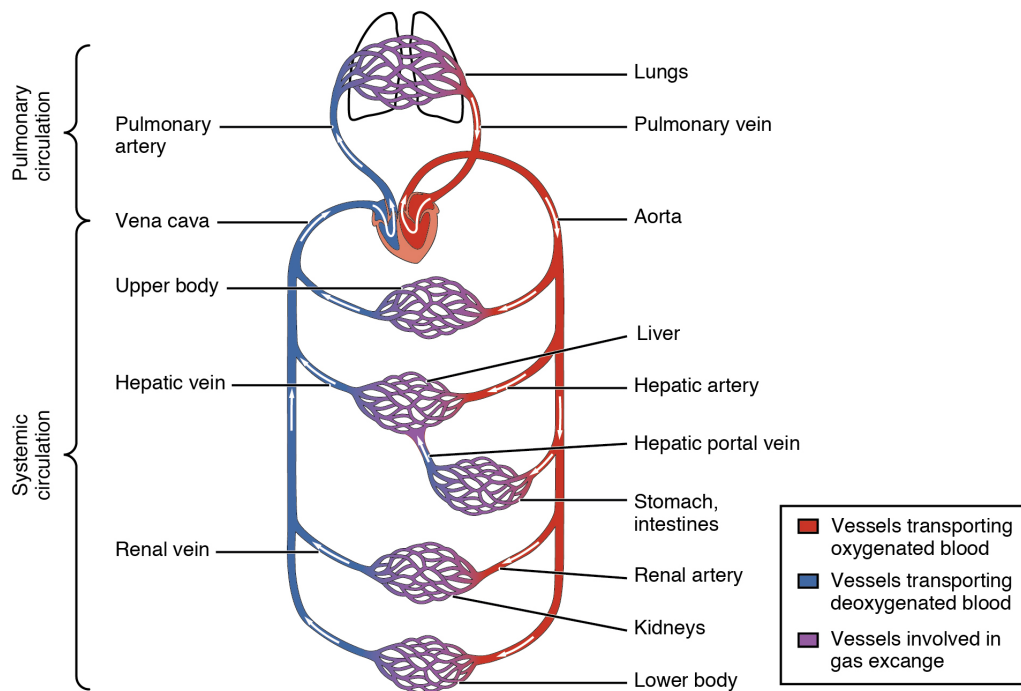
By the end of this section, you will be able to:

- Compare and contrast the three tunics that make up the walls of most blood vessels
- Distinguish between elastic arteries, muscular arteries, and arterioles on the basis of structure, location, and function
- Describe the basic structure of a capillary bed, from the supplying metarteriole to the venule into which it drains
- Explain the structure and function of venous valves in the large veins of the extremities

Blood is carried through the body via blood vessels. An artery is a blood vessel that carries blood away from the heart, where it branches into ever-smaller vessels. Eventually, the smallest arteries, vessels called arterioles, further branch into tiny capillaries, where nutrients and wastes are exchanged, and then combine with other vessels that exit capillaries to form venules, small blood vessels that carry blood to a vein, a larger blood vessel that returns blood to the heart.

Arteries and veins transport blood in two distinct circuits: the systemic circuit and the pulmonary circuit ([\[link\]](#)). Systemic arteries provide blood rich in oxygen to the body's tissues. The blood returned to the heart through systemic veins has less oxygen, since much of the oxygen carried by the arteries has been delivered to the cells. In contrast, in the pulmonary circuit, arteries carry blood low in oxygen exclusively to the lungs for gas exchange. Pulmonary veins then return freshly oxygenated blood from the lungs to the heart to be pumped back out into systemic circulation. Although arteries and veins differ structurally and functionally, they share certain features.

Cardiovascular Circulation



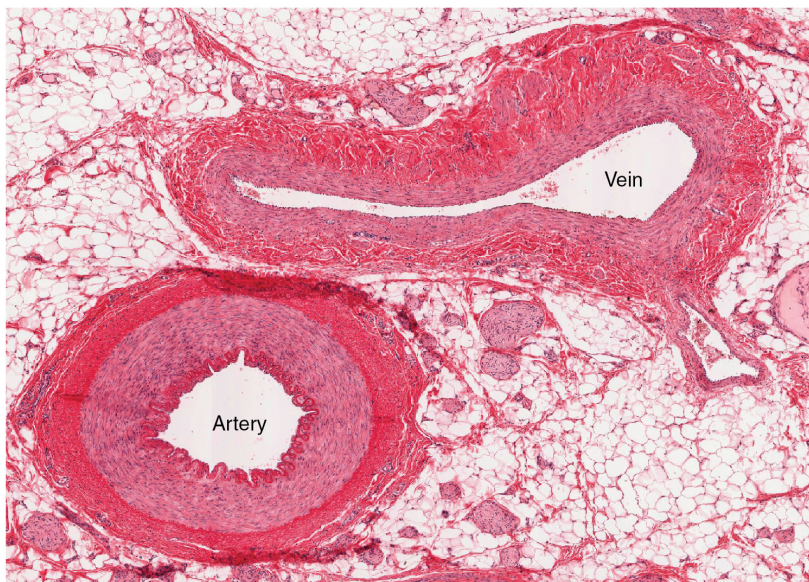
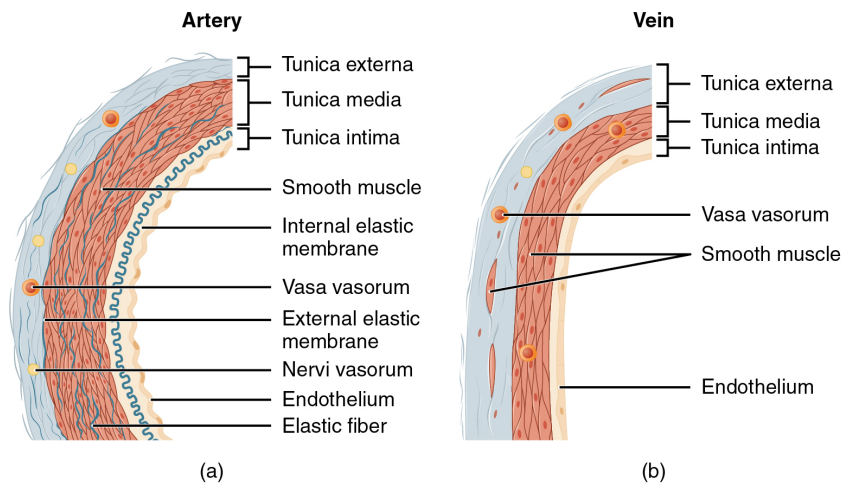
The pulmonary circuit moves blood from the right side of the heart to the lungs and back to the heart. The systemic circuit moves blood from the left side of the heart to the head and body and returns it to the right side of the heart to repeat the cycle. The arrows indicate the direction of blood flow, and the colors show the relative levels of oxygen concentration.

Shared Structures

Different types of blood vessels vary slightly in their structures, but they share the same general features. Arteries and arterioles have thicker walls than veins and venules because they are closer to the heart and receive blood that is surging at a far greater pressure ([link](#)). Each type of vessel has a **lumen**—a hollow passageway through which blood flows. Arteries have smaller lumens than veins, a characteristic that helps to maintain the pressure of blood moving through the system. Together, their thicker walls

and smaller diameters give arterial lumens a more rounded appearance in cross section than the lumens of veins.

Structure of Blood Vessels



(c)

(a) Arteries and (b) veins share the same general features, but the walls of arteries are much thicker because of the higher pressure of the blood that flows through them. (c) A micrograph shows the relative differences in thickness. LM \times 160. (Micrograph provided by the Regents of the University of Michigan Medical School \copyright 2012)

By the time blood has passed through capillaries and entered venules, the pressure initially exerted upon it by heart contractions has diminished. In other words, in comparison to arteries, venules and veins withstand a much lower pressure from the blood that flows through them. Their walls are considerably thinner and their lumens are correspondingly larger in diameter, allowing more blood to flow with less vessel resistance. In addition, many veins of the body, particularly those of the limbs, contain valves that assist the unidirectional flow of blood toward the heart. This is critical because blood flow becomes sluggish in the extremities, as a result of the lower pressure and the effects of gravity.

The walls of arteries and veins are largely composed of living cells and their products (including collagenous and elastic fibers); the cells require nourishment and produce waste. Since blood passes through the larger vessels relatively quickly, there is limited opportunity for blood in the lumen of the vessel to provide nourishment to or remove waste from the vessel's cells. Further, the walls of the larger vessels are too thick for nutrients to diffuse through to all of the cells. Larger arteries and veins contain small blood vessels within their walls known as the **vasa vasorum**—literally “vessels of the vessel”—to provide them with this critical exchange. Since the pressure within arteries is relatively high, the vasa vasorum must function in the outer layers of the vessel (see [\[link\]](#)) or the pressure exerted by the blood passing through the vessel would collapse it, preventing any exchange from occurring. The lower pressure within veins allows the vasa vasorum to be located closer to the lumen. The restriction of the vasa vasorum to the outer layers of arteries is thought to be one reason that arterial diseases are more common than venous diseases, since its location makes it more difficult to nourish the cells of the arteries and remove waste products. There are also minute nerves within the walls of both types of vessels that control the contraction and dilation of smooth muscle. These minute nerves are known as the nervi vasorum.

Both arteries and veins have the same three distinct tissue layers, called tunics (from the Latin term *tunica*), for the garments first worn by ancient Romans; the term tunic is also used for some modern garments. From the

most interior layer to the outer, these tunics are the tunica intima, the tunica media, and the tunica externa (see [\[link\]](#)). [\[link\]](#) compares and contrasts the tunics of the arteries and veins.

| Comparison of Tunics in Arteries and Veins | | |
|--|--|--|
| | Arteries | Veins |
| General appearance | Thick walls with small lumens Generally appear rounded | Thin walls with large lumens Generally appear flattened |
| Tunica intima | Endothelium usually appears wavy due to constriction of smooth muscle Internal elastic membrane present in larger vessels | Endothelium appears smooth Internal elastic membrane absent |

| Comparison of Tunics in Arteries and Veins | | |
|---|--|---|
| | Arteries | Veins |
| Tunica media | <p>Normally the thickest layer in arteries</p> <p>Smooth muscle cells and elastic fibers predominate (the proportions of these vary with distance from the heart)</p> <p>External elastic membrane present in larger vessels</p> | <p>Normally thinner than the tunica externa</p> <p>Smooth muscle cells and collagenous fibers predominate</p> <p>Nervi vasorum and vasa vasorum present</p> <p>External elastic membrane absent</p> |
| Tunica externa | <p>Normally thinner than the tunica media in all but the largest arteries</p> <p>Collagenous and elastic fibers</p> <p>Nervi vasorum and vasa vasorum present</p> | <p>Normally the thickest layer in veins</p> <p>Collagenous and smooth fibers predominate</p> <p>Some smooth muscle fibers</p> <p>Nervi vasorum and vasa vasorum present</p> |

Tunica Intima

The **tunica intima** (also called the tunica interna) is composed of epithelial and connective tissue layers. Lining the tunica intima is the specialized simple squamous epithelium called the endothelium, which is continuous throughout the entire vascular system, including the lining of the chambers of the heart. Damage to this endothelial lining and exposure of blood to the collagenous fibers beneath is one of the primary causes of clot formation. Until recently, the endothelium was viewed simply as the boundary between the blood in the lumen and the walls of the vessels. Recent studies, however, have shown that it is physiologically critical to such activities as helping to regulate capillary exchange and altering blood flow. The endothelium releases local chemicals called endothelins that can constrict the smooth muscle within the walls of the vessel to increase blood pressure. Uncompensated overproduction of endothelins may contribute to hypertension (high blood pressure) and cardiovascular disease.

Next to the endothelium is the basement membrane, or basal lamina, that effectively binds the endothelium to the connective tissue. The basement membrane provides strength while maintaining flexibility, and it is permeable, allowing materials to pass through it. The thin outer layer of the tunica intima contains a small amount of areolar connective tissue that consists primarily of elastic fibers to provide the vessel with additional flexibility; it also contains some collagenous fibers to provide additional strength.

In larger arteries, there is also a thick, distinct layer of elastic fibers known as the **internal elastic membrane** (also called the internal elastic lamina) at the boundary with the tunica media. Like the other components of the tunica intima, the internal elastic membrane provides structure while allowing the vessel to stretch. It is permeated with small openings that allow exchange of materials between the tunics. The internal elastic membrane is not apparent in veins. In addition, many veins, particularly in the lower limbs, contain valves formed by sections of thickened endothelium that are reinforced with connective tissue, extending into the lumen.

Under the microscope, the lumen and the entire tunica intima of a vein will appear smooth, whereas those of an artery will normally appear wavy because of the partial constriction of the smooth muscle in the tunica media, the next layer of blood vessel walls.

Tunica Media

The **tunica media** is the substantial middle layer of the vessel wall (see [\[link\]](#)). It is generally the thickest layer in arteries, and it is much thicker in arteries than it is in veins. The tunica media consists of layers of smooth muscle supported by connective tissue that is primarily made up of elastic fibers, most of which are arranged in circular sheets. Toward the outer portion of the tunic, there are also layers of longitudinal muscle. Contraction and relaxation of the circular muscles decrease and increase the diameter of the vessel lumen, respectively. Specifically in arteries, **vasoconstriction** decreases blood flow as the smooth muscle in the walls of the tunica media contracts, making the lumen narrower and increasing blood pressure. Similarly, **vasodilation** increases blood flow as the smooth muscle relaxes, allowing the lumen to widen and blood pressure to drop. Both vasoconstriction and vasodilation are regulated in part by small vascular nerves, known as **nervi vasorum**, or “nerves of the vessel,” that run within the walls of blood vessels. These are generally all sympathetic fibers, although some trigger vasodilation and others induce vasoconstriction, depending upon the nature of the neurotransmitter and receptors located on the target cell. Parasympathetic stimulation does trigger vasodilation as well as erection during sexual arousal in the external genitalia of both sexes. Nervous control over vessels tends to be more generalized than the specific targeting of individual blood vessels. Local controls, discussed later, account for this phenomenon. (Seek additional content for more information on these dynamic aspects of the autonomic nervous system.) Hormones and local chemicals also control blood vessels. Together, these neural and chemical mechanisms reduce or increase blood flow in response to changing body conditions, from exercise to hydration. Regulation of both blood flow and blood pressure is discussed in detail later in this chapter.

The smooth muscle layers of the tunica media are supported by a framework of collagenous fibers that also binds the tunica media to the inner and outer tunics. Along with the collagenous fibers are large numbers of elastic fibers that appear as wavy lines in prepared slides. Separating the tunica media from the outer tunica externa in larger arteries is the **external elastic membrane** (also called the external elastic lamina), which also appears wavy in slides. This structure is not usually seen in smaller arteries, nor is it seen in veins.

Tunica Externa

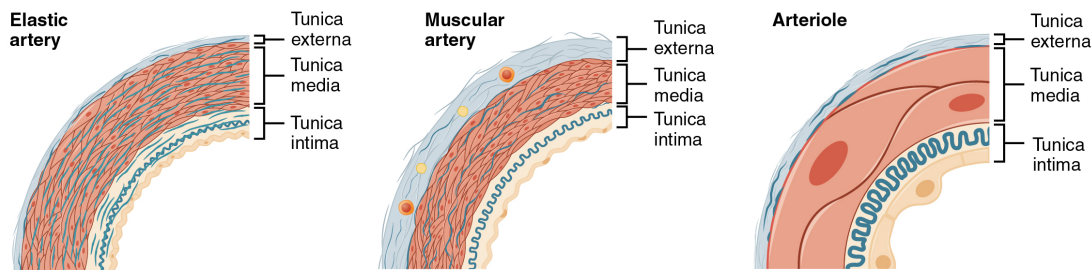
The outer tunic, the **tunica externa** (also called the tunica adventitia), is a substantial sheath of connective tissue composed primarily of collagenous fibers. Some bands of elastic fibers are found here as well. The tunica externa in veins also contains groups of smooth muscle fibers. This is normally the thickest tunic in veins and may be thicker than the tunica media in some larger arteries. The outer layers of the tunica externa are not distinct but rather blend with the surrounding connective tissue outside the vessel, helping to hold the vessel in relative position. If you are able to palpate some of the superficial veins on your upper limbs and try to move them, you will find that the tunica externa prevents this. If the tunica externa did not hold the vessel in place, any movement would likely result in disruption of blood flow.

Arteries

An **artery** is a blood vessel that conducts blood away from the heart. All arteries have relatively thick walls that can withstand the high pressure of blood ejected from the heart. However, those close to the heart have the thickest walls, containing a high percentage of elastic fibers in all three of their tunics. This type of artery is known as an **elastic artery** ([\[link\]](#)). Vessels larger than 10 mm in diameter are typically elastic. Their abundant elastic fibers allow them to expand, as blood pumped from the ventricles passes through them, and then to recoil after the surge has passed. If artery walls were rigid and unable to expand and recoil, their resistance to blood

flow would greatly increase and blood pressure would rise to even higher levels, which would in turn require the heart to pump harder to increase the volume of blood expelled by each pump (the stroke volume) and maintain adequate pressure and flow. Artery walls would have to become even thicker in response to this increased pressure. The elastic recoil of the vascular wall helps to maintain the pressure gradient that drives the blood through the arterial system. An elastic artery is also known as a conducting artery, because the large diameter of the lumen enables it to accept a large volume of blood from the heart and conduct it to smaller branches.

Types of Arteries and Arterioles



Comparison of the walls of an elastic artery, a muscular artery, and an arteriole is shown. In terms of scale, the diameter of an arteriole is measured in micrometers compared to millimeters for elastic and muscular arteries.

Farther from the heart, where the surge of blood has dampened, the percentage of elastic fibers in an artery's tunica intima decreases and the amount of smooth muscle in its tunica media increases. The artery at this point is described as a **muscular artery**. The diameter of muscular arteries typically ranges from 0.1 mm to 10 mm. Their thick tunica media allows muscular arteries to play a leading role in vasoconstriction. In contrast, their decreased quantity of elastic fibers limits their ability to expand. Fortunately, because the blood pressure has eased by the time it reaches these more distant vessels, elasticity has become less important.

Notice that although the distinctions between elastic and muscular arteries are important, there is no "line of demarcation" where an elastic artery suddenly becomes muscular. Rather, there is a gradual transition as the

vascular tree repeatedly branches. In turn, muscular arteries branch to distribute blood to the vast network of arterioles. For this reason, a muscular artery is also known as a distributing artery.

Arterioles

An **arteriole** is a very small artery that leads to a capillary. Arterioles have the same three tunics as the larger vessels, but the thickness of each is greatly diminished. The critical endothelial lining of the tunica intima is intact. The tunica media is restricted to one or two smooth muscle cell layers in thickness. The tunica externa remains but is very thin (see [\[link\]](#)).

With a lumen averaging 30 micrometers or less in diameter, arterioles are critical in slowing down—or resisting—blood flow and, thus, causing a substantial drop in blood pressure. Because of this, you may see them referred to as resistance vessels. The muscle fibers in arterioles are normally slightly contracted, causing arterioles to maintain a consistent muscle tone—in this case referred to as vascular tone—in a similar manner to the muscular tone of skeletal muscle. In reality, all blood vessels exhibit vascular tone due to the partial contraction of smooth muscle. The importance of the arterioles is that they will be the primary site of both resistance and regulation of blood pressure. The precise diameter of the lumen of an arteriole at any given moment is determined by neural and chemical controls, and vasoconstriction and vasodilation in the arterioles are the primary mechanisms for distribution of blood flow.

Capillaries

A **capillary** is a microscopic channel that supplies blood to the tissues themselves, a process called **perfusion**. Exchange of gases and other substances occurs in the capillaries between the blood and the surrounding cells and their tissue fluid (interstitial fluid). The diameter of a capillary lumen ranges from 5–10 micrometers; the smallest are just barely wide enough for an erythrocyte to squeeze through. Flow through capillaries is often described as **microcirculation**.

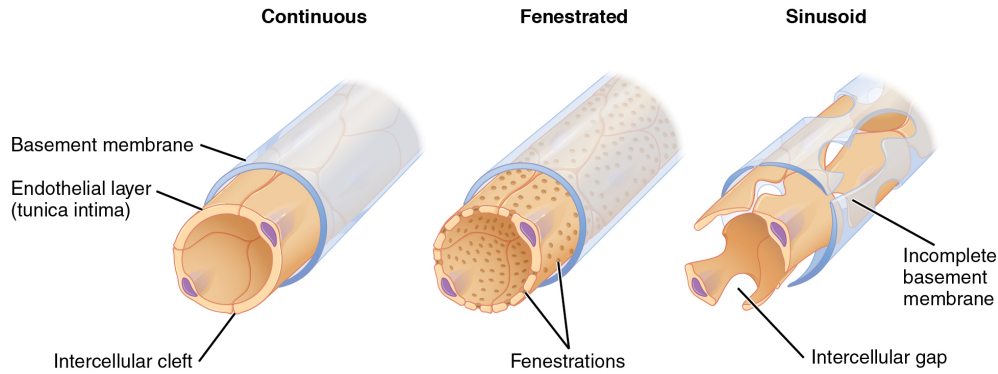
The wall of a capillary consists of the endothelial layer surrounded by a basement membrane with occasional smooth muscle fibers. There is some variation in wall structure: In a large capillary, several endothelial cells bordering each other may line the lumen; in a small capillary, there may be only a single cell layer that wraps around to contact itself.

For capillaries to function, their walls must be leaky, allowing substances to pass through. There are three major types of capillaries, which differ according to their degree of “leakiness:” continuous, fenestrated, and sinusoid capillaries ([link](#)).

Continuous Capillaries

The most common type of capillary, the **continuous capillary**, is found in almost all vascularized tissues. Continuous capillaries are characterized by a complete endothelial lining with tight junctions between endothelial cells. Although a tight junction is usually impermeable and only allows for the passage of water and ions, they are often incomplete in capillaries, leaving intercellular clefts that allow for exchange of water and other very small molecules between the blood plasma and the interstitial fluid. Substances that can pass between cells include metabolic products, such as glucose, water, and small hydrophobic molecules like gases and hormones, as well as various leukocytes. Continuous capillaries not associated with the brain are rich in transport vesicles, contributing to either endocytosis or exocytosis. Those in the brain are part of the blood-brain barrier. Here, there are tight junctions and no intercellular clefts, plus a thick basement membrane and astrocyte extensions called end feet; these structures combine to prevent the movement of nearly all substances.

Types of Capillaries



The three major types of capillaries: continuous, fenestrated, and sinusoid.

Fenestrated Capillaries

A **fenestrated capillary** is one that has pores (or fenestrations) in addition to tight junctions in the endothelial lining. These make the capillary permeable to larger molecules. The number of fenestrations and their degree of permeability vary, however, according to their location.

Fenestrated capillaries are common in the small intestine, which is the primary site of nutrient absorption, as well as in the kidneys, which filter the blood. They are also found in the choroid plexus of the brain and many endocrine structures, including the hypothalamus, pituitary, pineal, and thyroid glands.

Sinusoid Capillaries

A **sinusoid capillary** (or sinusoid) is the least common type of capillary. Sinusoid capillaries are flattened, and they have extensive intercellular gaps and incomplete basement membranes, in addition to intercellular clefts and fenestrations. This gives them an appearance not unlike Swiss cheese. These very large openings allow for the passage of the largest molecules, including plasma proteins and even cells. Blood flow through sinusoids is

very slow, allowing more time for exchange of gases, nutrients, and wastes. Sinusoids are found in the liver and spleen, bone marrow, lymph nodes (where they carry lymph, not blood), and many endocrine glands including the pituitary and adrenal glands. Without these specialized capillaries, these organs would not be able to provide their myriad of functions. For example, when bone marrow forms new blood cells, the cells must enter the blood supply and can only do so through the large openings of a sinusoid capillary; they cannot pass through the small openings of continuous or fenestrated capillaries. The liver also requires extensive specialized sinusoid capillaries in order to process the materials brought to it by the hepatic portal vein from both the digestive tract and spleen, and to release plasma proteins into circulation.

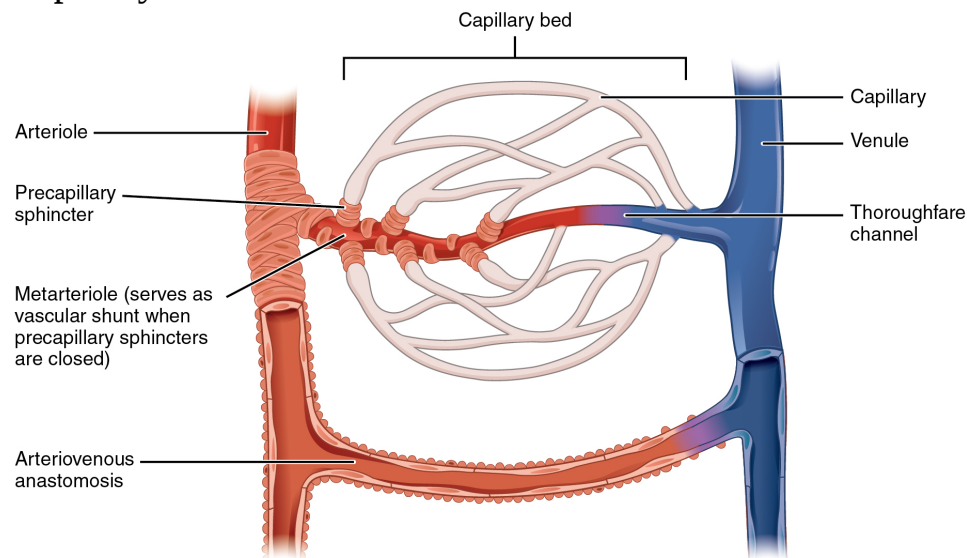
Metarterioles and Capillary Beds

A **metarteriole** is a type of vessel that has structural characteristics of both an arteriole and a capillary. Slightly larger than the typical capillary, the smooth muscle of the tunica media of the metarteriole is not continuous but forms rings of smooth muscle (sphincters) prior to the entrance to the capillaries. Each metarteriole arises from a terminal arteriole and branches to supply blood to a **capillary bed** that may consist of 10–100 capillaries.

The **precapillary sphincters**, circular smooth muscle cells that surround the capillary at its origin with the metarteriole, tightly regulate the flow of blood from a metarteriole to the capillaries it supplies. Their function is critical: If all of the capillary beds in the body were to open simultaneously, they would collectively hold every drop of blood in the body and there would be none in the arteries, arterioles, venules, veins, or the heart itself. Normally, the precapillary sphincters are closed. When the surrounding tissues need oxygen and have excess waste products, the precapillary sphincters open, allowing blood to flow through and exchange to occur before closing once more ([\[link\]](#)). If all of the precapillary sphincters in a capillary bed are closed, blood will flow from the metarteriole directly into a **thoroughfare channel** and then into the venous circulation, bypassing the capillary bed entirely. This creates what is known as a **vascular shunt**. In addition, an **arteriovenous anastomosis** may bypass the capillary bed and lead directly to the venous system.

Although you might expect blood flow through a capillary bed to be smooth, in reality, it moves with an irregular, pulsating flow. This pattern is called **vasomotion** and is regulated by chemical signals that are triggered in response to changes in internal conditions, such as oxygen, carbon dioxide, hydrogen ion, and lactic acid levels. For example, during strenuous exercise when oxygen levels decrease and carbon dioxide, hydrogen ion, and lactic acid levels all increase, the capillary beds in skeletal muscle are open, as they would be in the digestive system when nutrients are present in the digestive tract. During sleep or rest periods, vessels in both areas are largely closed; they open only occasionally to allow oxygen and nutrient supplies to travel to the tissues to maintain basic life processes.

Capillary Bed



In a capillary bed, arterioles give rise to metarterioles.

Precapillary sphincters located at the junction of a metarteriole with a capillary regulate blood flow. A thoroughfare channel connects the metarteriole to a venule. An arteriovenous anastomosis, which directly connects the arteriole with the venule, is shown at the bottom.

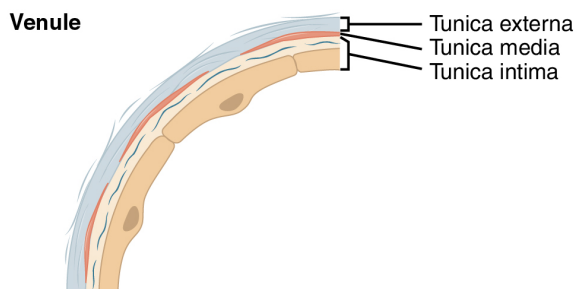
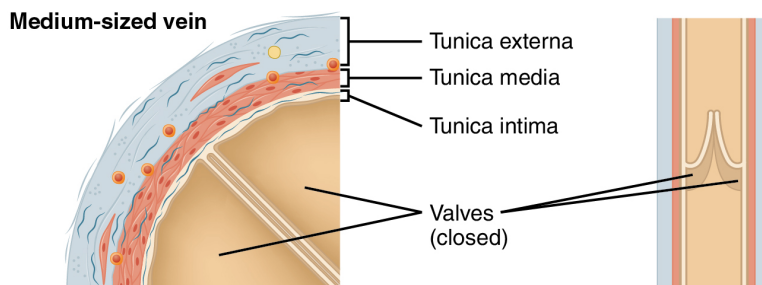
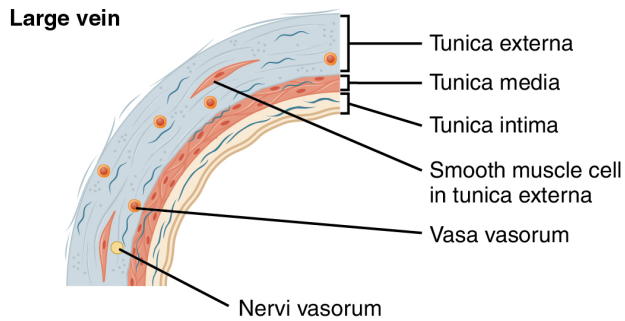
Venules

A **venule** is an extremely small vein, generally 8–100 micrometers in diameter. Postcapillary venules join multiple capillaries exiting from a capillary bed. Multiple venules join to form veins. The walls of venules consist of endothelium, a thin middle layer with a few muscle cells and elastic fibers, plus an outer layer of connective tissue fibers that constitute a very thin tunica externa ([\[link\]](#)). Venules as well as capillaries are the primary sites of emigration or diapedesis, in which the white blood cells adhere to the endothelial lining of the vessels and then squeeze through adjacent cells to enter the tissue fluid.

Veins

A **vein** is a blood vessel that conducts blood toward the heart. Compared to arteries, veins are thin-walled vessels with large and irregular lumens (see [\[link\]](#)). Because they are low-pressure vessels, larger veins are commonly equipped with valves that promote the unidirectional flow of blood toward the heart and prevent backflow toward the capillaries caused by the inherent low blood pressure in veins as well as the pull of gravity. [\[link\]](#) compares the features of arteries and veins.

Comparison of Veins and Venules



Many veins have valves to prevent back flow of blood, whereas venules do not. In terms of scale, the diameter of a venule is measured in micrometers compared to millimeters for veins.

| Comparison of Arteries and Veins | | |
|---|--|---|
| | Arteries | Veins |
| Direction of blood flow | Conducts blood away from the heart | Conducts blood toward the heart |
| General appearance | Rounded | Irregular, often collapsed |
| Pressure | High | Low |
| Wall thickness | Thick | Thin |
| Relative oxygen concentration | Higher in systemic arteries Lower in pulmonary arteries | Lower in systemic veins Higher in pulmonary veins |
| Valves | Not present | Present most commonly in limbs and in veins inferior to the heart |

Note:

Disorders of the...

Cardiovascular System: Edema and Varicose Veins

Despite the presence of valves and the contributions of other anatomical and physiological adaptations we will cover shortly, over the course of a day, some blood will inevitably pool, especially in the lower limbs, due to the pull of gravity. Any blood that accumulates in a vein will increase the

pressure within it, which can then be reflected back into the smaller veins, venules, and eventually even the capillaries. Increased pressure will promote the flow of fluids out of the capillaries and into the interstitial fluid. The presence of excess tissue fluid around the cells leads to a condition called edema.

Most people experience a daily accumulation of tissue fluid, especially if they spend much of their work life on their feet (like most health professionals). However, clinical edema goes beyond normal swelling and requires medical treatment. Edema has many potential causes, including hypertension and heart failure, severe protein deficiency, renal failure, and many others. In order to treat edema, which is a sign rather than a discrete disorder, the underlying cause must be diagnosed and alleviated.

Varicose Veins



Varicose veins are commonly found in the lower limbs. (credit: Thomas Kriesse)

Edema may be accompanied by varicose veins, especially in the superficial veins of the legs ([\[link\]](#)). This disorder arises when defective valves allow blood to accumulate within the veins, causing them to distend, twist, and become visible on the surface of the integument. Varicose veins may occur in both sexes, but are more common in women and are often related to pregnancy. More than simple cosmetic blemishes, varicose veins are often painful and sometimes itchy or throbbing. Without treatment, they tend to grow worse over time. The use of support hose, as well as elevating the feet and legs whenever possible, may be helpful in alleviating this condition. Laser surgery and interventional radiologic procedures can reduce the size and severity of varicose veins. Severe cases may require conventional surgery to remove the damaged vessels. As there are typically redundant circulation patterns, that is, anastomoses, for the smaller and more superficial veins, removal does not typically impair the circulation. There is evidence that patients with varicose veins suffer a greater risk of developing a thrombus or clot.

Veins as Blood Reservoirs

In addition to their primary function of returning blood to the heart, veins may be considered blood reservoirs, since systemic veins contain approximately 64 percent of the blood volume at any given time ([\[link\]](#)). Their ability to hold this much blood is due to their high **capacitance**, that is, their capacity to distend (expand) readily to store a high volume of blood, even at a low pressure. The large lumens and relatively thin walls of veins make them far more distensible than arteries; thus, they are said to be **capacitance vessels**.

Distribution of Blood Flow

| | | |
|-----------------------------|-----------------------------|---|
| Systemic circulation 84% | Systemic veins 64% | Large veins 18% |
| | | Large venous networks (liver, bone marrow, and integument) 21% |
| | | Venules and medium-sized veins 25% |
| | Systemic arteries 13% | Arterioles 2% |
| | | Muscular arteries 5% |
| | | Elastic arteries 4% |
| | | Aorta 2% |
| | Systemic capillaries 7% | Systemic capillaries 7% |
| Pulmonary circulation 9% | Pulmonary veins 4% | |
| | Pulmonary capillaries 2% | |
| | Pulmonary arteries 3% | |
| Heart 7% | | |

When blood flow needs to be redistributed to other portions of the body, the vasomotor center located in the medulla oblongata sends sympathetic stimulation to the smooth muscles in the walls of the veins, causing constriction—or in this case, venoconstriction. Less dramatic than the vasoconstriction seen in smaller arteries and arterioles, venoconstriction may be likened to a “stiffening” of the vessel wall. This increases pressure on the blood within the veins, speeding its return to the heart. As you will note in [\[link\]](#), approximately 21 percent of the venous blood is located in venous networks within the liver, bone marrow, and integument. This volume of blood is referred to as **venous reserve**. Through venoconstriction, this “reserve” volume of blood can get back to the heart more quickly for redistribution to other parts of the circulation.

Note:

Career Connection

Vascular Surgeons and Technicians

Vascular surgery is a specialty in which the physician deals primarily with diseases of the vascular portion of the cardiovascular system. This includes repair and replacement of diseased or damaged vessels, removal of plaque from vessels, minimally invasive procedures including the insertion of venous catheters, and traditional surgery. Following completion of medical school, the physician generally completes a 5-year surgical residency followed by an additional 1 to 2 years of vascular specialty training. In the United States, most vascular surgeons are members of the Society of Vascular Surgery.

Vascular technicians are specialists in imaging technologies that provide information on the health of the vascular system. They may also assist physicians in treating disorders involving the arteries and veins. This profession often overlaps with cardiovascular technology, which would also include treatments involving the heart. Although recognized by the American Medical Association, there are currently no licensing requirements for vascular technicians, and licensing is voluntary. Vascular technicians typically have an Associate's degree or certificate, involving 18 months to 2 years of training. The United States Bureau of Labor projects this profession to grow by 29 percent from 2010 to 2020.

Note:



Visit this [site](#) to learn more about vascular surgery.

Note:



Visit this [site](#) to learn more about vascular technicians.

Chapter Review

Blood pumped by the heart flows through a series of vessels known as arteries, arterioles, capillaries, venules, and veins before returning to the heart. Arteries transport blood away from the heart and branch into smaller vessels, forming arterioles. Arterioles distribute blood to capillary beds, the sites of exchange with the body tissues. Capillaries lead back to small vessels known as venules that flow into the larger veins and eventually back to the heart.

The arterial system is a relatively high-pressure system, so arteries have thick walls that appear round in cross section. The venous system is a lower-pressure system, containing veins that have larger lumens and thinner walls. They often appear flattened. Arteries, arterioles, venules, and veins are composed of three tunics known as the tunica intima, tunica media, and tunica externa. Capillaries have only a tunica intima layer. The tunica intima is a thin layer composed of a simple squamous epithelium known as endothelium and a small amount of connective tissue. The tunica media is a thicker area composed of variable amounts of smooth muscle and connective tissue. It is the thickest layer in all but the largest arteries. The tunica externa is primarily a layer of connective tissue, although in veins, it also contains some smooth muscle. Blood flow through vessels can be dramatically influenced by vasoconstriction and vasodilation in their walls.

Review Questions

Exercise:

Problem: The endothelium is found in the _____.

- a. tunica intima
- b. tunica media
- c. tunica externa
- d. lumen

Solution:

A

Exercise:

Problem: Nervi vasorum control _____.

- a. vasoconstriction
- b. vasodilation
- c. capillary permeability
- d. both vasoconstriction and vasodilation

Solution:

D

Exercise:

Problem:

Closer to the heart, arteries would be expected to have a higher percentage of _____.

- a. endothelium
 - b. smooth muscle fibers
 - c. elastic fibers
 - d. collagenous fibers
-

Solution:

C

Exercise:

Problem: Which of the following best describes veins?

- a. thick walled, small lumens, low pressure, lack valves
 - b. thin walled, large lumens, low pressure, have valves
 - c. thin walled, small lumens, high pressure, have valves
 - d. thick walled, large lumens, high pressure, lack valves
-

Solution:

B

Exercise:

Problem:

An especially leaky type of capillary found in the liver and certain other tissues is called a _____.

- a. capillary bed
 - b. fenestrated capillary
 - c. sinusoid capillary
 - d. metarteriole
-

Solution:

C

Critical Thinking Questions

Exercise:

Problem: Arterioles are often referred to as resistance vessels. Why?

Solution:

Arterioles receive blood from arteries, which are vessels with a much larger lumen. As their own lumen averages just 30 micrometers or less, arterioles are critical in slowing down—or resisting—blood flow. The arterioles can also constrict or dilate, which varies their resistance, to help distribute blood flow to the tissues.

Exercise:

Problem:

Cocaine use causes vasoconstriction. Is this likely to increase or decrease blood pressure, and why?

Solution:

Vasoconstriction causes the lumens of blood vessels to narrow. This increases the pressure of the blood flowing within the vessel.

Exercise:

Problem:

A blood vessel with a few smooth muscle fibers and connective tissue, and only a very thin tunica externa conducts blood toward the heart. What type of vessel is this?

Solution:

This is a venule.

Glossary

arteriole

(also, resistance vessel) very small artery that leads to a capillary

arteriovenous anastomosis

short vessel connecting an arteriole directly to a venule and bypassing the capillary beds

artery

blood vessel that conducts blood away from the heart; may be a conducting or distributing vessel

capacitance

ability of a vein to distend and store blood

capacitance vessels

veins

capillary

smallest of blood vessels where physical exchange occurs between the blood and tissue cells surrounded by interstitial fluid

capillary bed

network of 10–100 capillaries connecting arterioles to venules

continuous capillary

most common type of capillary, found in virtually all tissues except epithelia and cartilage; contains very small gaps in the endothelial lining that permit exchange

elastic artery

(also, conducting artery) artery with abundant elastic fibers located closer to the heart, which maintains the pressure gradient and conducts blood to smaller branches

external elastic membrane

membrane composed of elastic fibers that separates the tunica media from the tunica externa; seen in larger arteries

fenestrated capillary

type of capillary with pores or fenestrations in the endothelium that allow for rapid passage of certain small materials

internal elastic membrane

membrane composed of elastic fibers that separates the tunica intima from the tunica media; seen in larger arteries

lumen

interior of a tubular structure such as a blood vessel or a portion of the alimentary canal through which blood, chyme, or other substances travel

metarteriole

short vessel arising from a terminal arteriole that branches to supply a capillary bed

microcirculation

blood flow through the capillaries

muscular artery

(also, distributing artery) artery with abundant smooth muscle in the tunica media that branches to distribute blood to the arteriole network

nervi vasorum

small nerve fibers found in arteries and veins that trigger contraction of the smooth muscle in their walls

perfusion

distribution of blood into the capillaries so the tissues can be supplied

precapillary sphincters

circular rings of smooth muscle that surround the entrance to a capillary and regulate blood flow into that capillary

sinusoid capillary

rarest type of capillary, which has extremely large intercellular gaps in the basement membrane in addition to clefts and fenestrations; found in areas such as the bone marrow and liver where passage of large molecules occurs

thoroughfare channel

continuation of the metarteriole that enables blood to bypass a capillary bed and flow directly into a venule, creating a vascular shunt

tunica externa

(also, tunica adventitia) outermost layer or tunic of a vessel (except capillaries)

tunica intima

(also, tunica interna) innermost lining or tunic of a vessel

tunica media

middle layer or tunic of a vessel (except capillaries)

vasa vasorum

small blood vessels located within the walls or tunics of larger vessels that supply nourishment to and remove wastes from the cells of the vessels

vascular shunt

continuation of the metarteriole and thoroughfare channel that allows blood to bypass the capillary beds to flow directly from the arterial to the venous circulation

vasoconstriction

constriction of the smooth muscle of a blood vessel, resulting in a decreased vascular diameter

vasodilation

relaxation of the smooth muscle in the wall of a blood vessel, resulting in an increased vascular diameter

vasomotion

irregular, pulsating flow of blood through capillaries and related structures

vein

blood vessel that conducts blood toward the heart

venous reserve

volume of blood contained within systemic veins in the integument, bone marrow, and liver that can be returned to the heart for circulation, if needed

venule

small vessel leading from the capillaries to veins

Blood Flow, Blood Pressure, and Resistance

By the end of this section, you will be able to:

- Distinguish between systolic pressure, diastolic pressure, pulse pressure, and mean arterial pressure
- Describe the clinical measurement of pulse and blood pressure
- Identify and discuss five variables affecting arterial blood flow and blood pressure
- Discuss several factors affecting blood flow in the venous system

Blood flow refers to the movement of blood through a vessel, tissue, or organ, and is usually expressed in terms of volume of blood per unit of time. It is initiated by the contraction of the ventricles of the heart.

Ventricular contraction ejects blood into the major arteries, resulting in flow from regions of higher pressure to regions of lower pressure, as blood encounters smaller arteries and arterioles, then capillaries, then the venules and veins of the venous system. This section discusses a number of critical variables that contribute to blood flow throughout the body. It also discusses the factors that impede or slow blood flow, a phenomenon known as **resistance**.

As noted earlier, hydrostatic pressure is the force exerted by a fluid due to gravitational pull, usually against the wall of the container in which it is located. One form of hydrostatic pressure is **blood pressure**, the force exerted by blood upon the walls of the blood vessels or the chambers of the heart. Blood pressure may be measured in capillaries and veins, as well as the vessels of the pulmonary circulation; however, the term blood pressure without any specific descriptors typically refers to systemic arterial blood pressure—that is, the pressure of blood flowing in the arteries of the systemic circulation. In clinical practice, this pressure is measured in mm Hg and is usually obtained using the brachial artery of the arm.

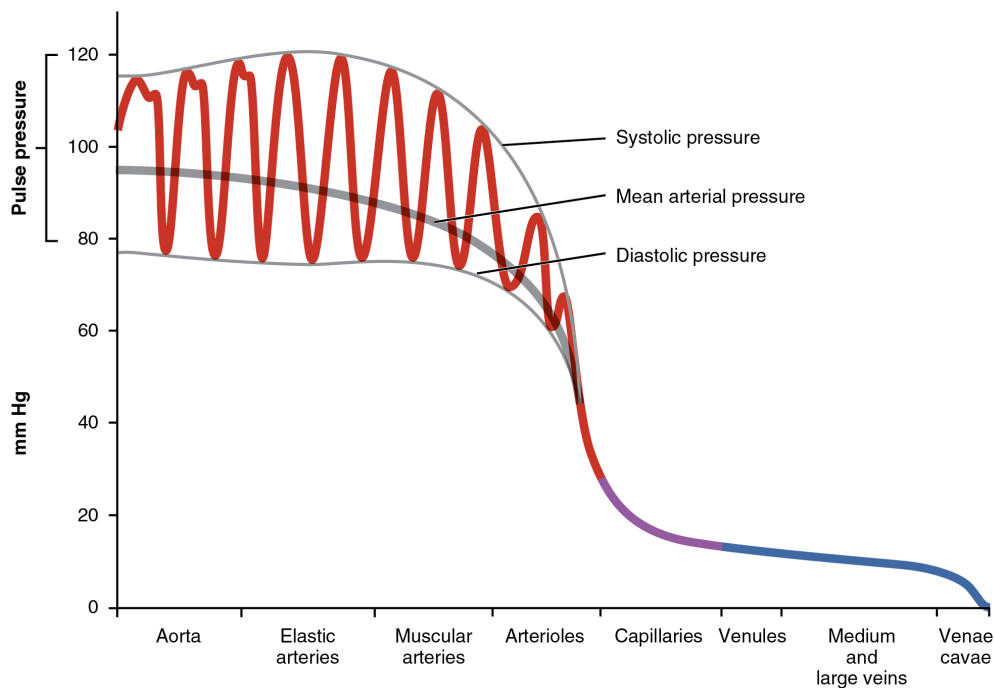
Components of Arterial Blood Pressure

Arterial blood pressure in the larger vessels consists of several distinct components ([link](#)): systolic and diastolic pressures, pulse pressure, and mean arterial pressure.

Systolic and Diastolic Pressures

When systemic arterial blood pressure is measured, it is recorded as a ratio of two numbers (e.g., 120/80 is a normal adult blood pressure), expressed as systolic pressure over diastolic pressure. The **systolic pressure** is the higher value (typically around 120 mm Hg) and reflects the arterial pressure resulting from the ejection of blood during ventricular contraction, or systole. The **diastolic pressure** is the lower value (usually about 80 mm Hg) and represents the arterial pressure of blood during ventricular relaxation, or diastole.

Systemic Blood Pressure



The graph shows the components of blood pressure throughout the blood vessels, including systolic, diastolic, mean arterial, and pulse pressures.

Pulse Pressure

As shown in [\[link\]](#), the difference between the systolic pressure and the diastolic pressure is the **pulse pressure**. For example, an individual with a systolic pressure of 120 mm Hg and a diastolic pressure of 80 mm Hg would have a pulse pressure of 40 mmHg.

Generally, a pulse pressure should be at least 25 percent of the systolic pressure. A pulse pressure below this level is described as low or narrow. This may occur, for example, in patients with a low stroke volume, which may be seen in congestive heart failure, stenosis of the aortic valve, or significant blood loss following trauma. In contrast, a high or wide pulse pressure is common in healthy people following strenuous exercise, when their resting pulse pressure of 30–40 mm Hg may increase temporarily to 100 mm Hg as stroke volume increases. A persistently high pulse pressure at or above 100 mm Hg may indicate excessive resistance in the arteries and can be caused by a variety of disorders. Chronic high resting pulse pressures can degrade the heart, brain, and kidneys, and warrant medical treatment.

Mean Arterial Pressure

Mean arterial pressure (MAP) represents the “average” pressure of blood in the arteries, that is, the average force driving blood into vessels that serve the tissues. Mean is a statistical concept and is calculated by taking the sum of the values divided by the number of values. Although complicated to measure directly and complicated to calculate, MAP can be approximated by adding the diastolic pressure to one-third of the pulse pressure or systolic pressure minus the diastolic pressure:

$$\text{MAP} = \text{diastolic BP} + \frac{(\text{systolic} - \text{diastolic BP})}{3}$$

In [\[link\]](#), this value is approximately $80 + (120 - 80) / 3$, or 93.33. Normally, the MAP falls within the range of 70–110 mm Hg. If the value falls below 60 mm Hg for an extended time, blood pressure will not be high enough to ensure circulation to and through the tissues, which results in **ischemia**, or insufficient blood flow. A condition called **hypoxia**,

inadequate oxygenation of tissues, commonly accompanies ischemia. The term hypoxemia refers to low levels of oxygen in systemic arterial blood. Neurons are especially sensitive to hypoxia and may die or be damaged if blood flow and oxygen supplies are not quickly restored.

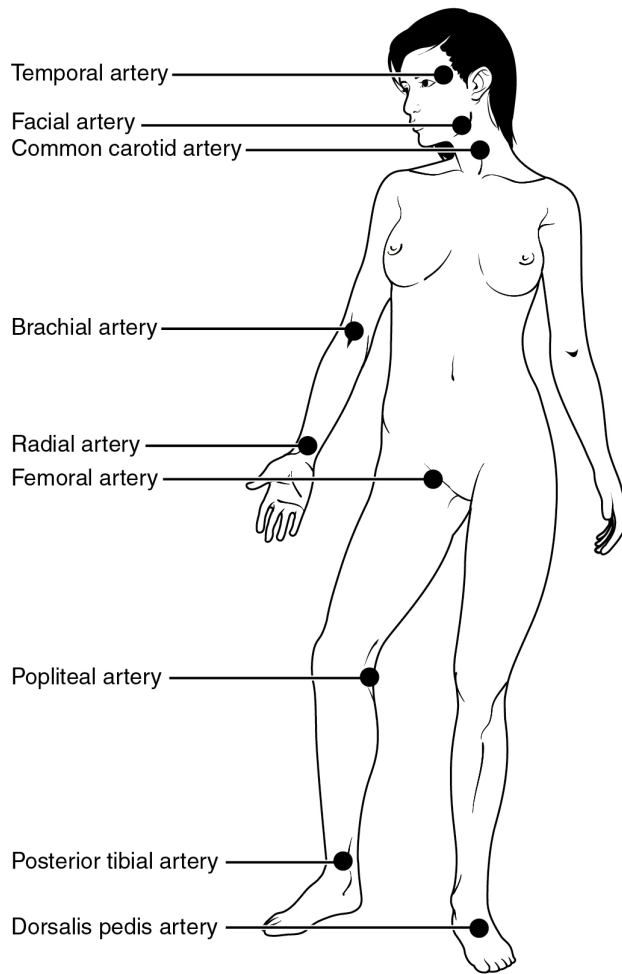
Pulse

After blood is ejected from the heart, elastic fibers in the arteries help maintain a high-pressure gradient as they expand to accommodate the blood, then recoil. This expansion and recoiling effect, known as the **pulse**, can be palpated manually or measured electronically. Although the effect diminishes over distance from the heart, elements of the systolic and diastolic components of the pulse are still evident down to the level of the arterioles.

Because pulse indicates heart rate, it is measured clinically to provide clues to a patient's state of health. It is recorded as beats per minute. Both the rate and the strength of the pulse are important clinically. A high or irregular pulse rate can be caused by physical activity or other temporary factors, but it may also indicate a heart condition. The pulse strength indicates the strength of ventricular contraction and cardiac output. If the pulse is strong, then systolic pressure is high. If it is weak, systolic pressure has fallen, and medical intervention may be warranted.

Pulse can be palpated manually by placing the tips of the fingers across an artery that runs close to the body surface and pressing lightly. While this procedure is normally performed using the radial artery in the wrist or the common carotid artery in the neck, any superficial artery that can be palpated may be used ([\[link\]](#)). Common sites to find a pulse include temporal and facial arteries in the head, brachial arteries in the upper arm, femoral arteries in the thigh, popliteal arteries behind the knees, posterior tibial arteries near the medial tarsal regions, and dorsalis pedis arteries in the feet. A variety of commercial electronic devices are also available to measure pulse.

Pulse Sites



The pulse is most readily measured at the radial artery, but can be measured at any of the pulse points shown.

Measurement of Blood Pressure

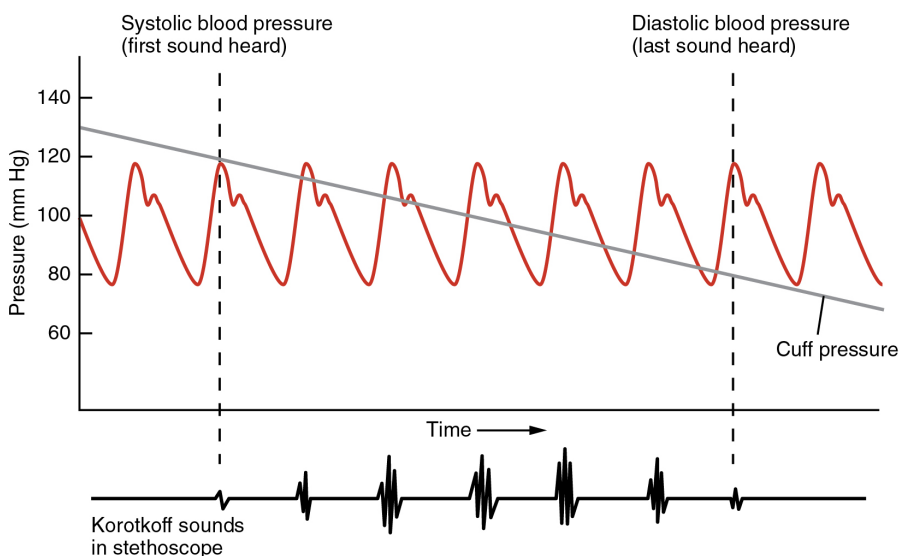
Blood pressure is one of the critical parameters measured on virtually every patient in every healthcare setting. The technique used today was developed more than 100 years ago by a pioneering Russian physician, Dr. Nikolai Korotkoff. Turbulent blood flow through the vessels can be heard as a soft ticking while measuring blood pressure; these sounds are known as

Korotkoff sounds. The technique of measuring blood pressure requires the use of a **sphygmomanometer** (a blood pressure cuff attached to a measuring device) and a stethoscope. The technique is as follows:

- The clinician wraps an inflatable cuff tightly around the patient's arm at about the level of the heart.
- The clinician squeezes a rubber pump to inject air into the cuff, raising pressure around the artery and temporarily cutting off blood flow into the patient's arm.
- The clinician places the stethoscope on the patient's antecubital region and, while gradually allowing air within the cuff to escape, listens for the Korotkoff sounds.

Although there are five recognized Korotkoff sounds, only two are normally recorded. Initially, no sounds are heard since there is no blood flow through the vessels, but as air pressure drops, the cuff relaxes, and blood flow returns to the arm. As shown in [\[link\]](#), the first sound heard through the stethoscope—the first Korotkoff sound—indicates systolic pressure. As more air is released from the cuff, blood is able to flow freely through the brachial artery and all sounds disappear. The point at which the last sound is heard is recorded as the patient's diastolic pressure.

Blood Pressure Measurement



When pressure in a sphygmomanometer cuff is released, a clinician can hear the Korotkoff sounds.

In this graph, a blood pressure tracing is aligned to a measurement of systolic and diastolic pressures.

The majority of hospitals and clinics have automated equipment for measuring blood pressure that work on the same principles. An even more recent innovation is a small instrument that wraps around a patient's wrist. The patient then holds the wrist over the heart while the device measures blood flow and records pressure.

Variables Affecting Blood Flow and Blood Pressure

Five variables influence blood flow and blood pressure:

- Cardiac output
- Compliance
- Volume of the blood
- Viscosity of the blood
- Blood vessel length and diameter

Recall that blood moves from higher pressure to lower pressure. It is pumped from the heart into the arteries at high pressure. If you increase pressure in the arteries (afterload), and cardiac function does not compensate, blood flow will actually decrease. In the venous system, the opposite relationship is true. Increased pressure in the veins does not decrease flow as it does in arteries, but actually increases flow. Since pressure in the veins is normally relatively low, for blood to flow back into the heart, the pressure in the atria during atrial diastole must be even lower. It normally approaches zero, except when the atria contract (see [\[link\]](#)).

Cardiac Output

Cardiac output is the measurement of blood flow from the heart through the ventricles, and is usually measured in liters per minute. Any factor that

causes cardiac output to increase, by elevating heart rate or stroke volume or both, will elevate blood pressure and promote blood flow. These factors include sympathetic stimulation, the catecholamines epinephrine and norepinephrine, thyroid hormones, and increased calcium ion levels. Conversely, any factor that decreases cardiac output, by decreasing heart rate or stroke volume or both, will decrease arterial pressure and blood flow. These factors include parasympathetic stimulation, elevated or decreased potassium ion levels, decreased calcium levels, anoxia, and acidosis.

Compliance

Compliance is the ability of any compartment to expand to accommodate increased content. A metal pipe, for example, is not compliant, whereas a balloon is. The greater the compliance of an artery, the more effectively it is able to expand to accommodate surges in blood flow without increased resistance or blood pressure. Veins are more compliant than arteries and can expand to hold more blood. When vascular disease causes stiffening of arteries, compliance is reduced and resistance to blood flow is increased. The result is more turbulence, higher pressure within the vessel, and reduced blood flow. This increases the work of the heart.

A Mathematical Approach to Factors Affecting Blood Flow

Jean Louis Marie Poiseuille was a French physician and physiologist who devised a mathematical equation describing blood flow and its relationship to known parameters. The same equation also applies to engineering studies of the flow of fluids. Although understanding the math behind the relationships among the factors affecting blood flow is not necessary to understand blood flow, it can help solidify an understanding of their relationships. Please note that even if the equation looks intimidating, breaking it down into its components and following the relationships will make these relationships clearer, even if you are weak in math. Focus on the three critical variables: radius (r), vessel length (λ), and viscosity (η).

Poiseuille's equation:

Equation:

$$\text{Blood flow} = \frac{\pi \Delta P r^4}{8\eta\lambda}$$

π is the Greek letter pi, used to represent the mathematical constant that is the ratio of a circle's circumference to its diameter. It may commonly be represented as 3.14, although the actual number extends to infinity.

ΔP represents the difference in pressure.

r^4 is the radius (one-half of the diameter) of the vessel to the fourth power.

η is the Greek letter eta and represents the viscosity of the blood.

λ is the Greek letter lambda and represents the length of a blood vessel.

One of several things this equation allows us to do is calculate the resistance in the vascular system. Normally this value is extremely difficult to measure, but it can be calculated from this known relationship:

Equation:

$$\text{Blood flow} = \frac{\Delta P}{\text{Resistance}}$$

If we rearrange this slightly,

Equation:

$$\text{Resistance} = \frac{\Delta P}{\text{Blood flow}}$$

Then by substituting Poiseuille's equation for blood flow:

Equation:

$$\text{Resistance} = \frac{8\eta\lambda}{\pi r^4}$$

By examining this equation, you can see that there are only three variables: viscosity, vessel length, and radius, since 8 and π are both constants. The important thing to remember is this: Two of these variables, viscosity and vessel length, will change slowly in the body. Only one of these factors, the radius, can be changed rapidly by vasoconstriction and vasodilation, thus dramatically impacting resistance and flow. Further, small changes in the radius will greatly affect flow, since it is raised to the fourth power in the equation.

We have briefly considered how cardiac output and blood volume impact blood flow and pressure; the next step is to see how the other variables (contraction, vessel length, and viscosity) articulate with Poiseuille's equation and what they can teach us about the impact on blood flow.

Blood Volume

The relationship between blood volume, blood pressure, and blood flow is intuitively obvious. Water may merely trickle along a creek bed in a dry season, but rush quickly and under great pressure after a heavy rain. Similarly, as blood volume decreases, pressure and flow decrease. As blood volume increases, pressure and flow increase.

Under normal circumstances, blood volume varies little. Low blood volume, called **hypovolemia**, may be caused by bleeding, dehydration, vomiting, severe burns, or some medications used to treat hypertension. It is important to recognize that other regulatory mechanisms in the body are so effective at maintaining blood pressure that an individual may be asymptomatic until 10–20 percent of the blood volume has been lost. Treatment typically includes intravenous fluid replacement.

Hypervolemia, excessive fluid volume, may be caused by retention of water and sodium, as seen in patients with heart failure, liver cirrhosis, some forms of kidney disease, hyperaldosteronism, and some glucocorticoid steroid treatments. Restoring homeostasis in these patients depends upon reversing the condition that triggered the hypervolemia.

Blood Viscosity

Viscosity is the thickness of fluids that affects their ability to flow. Clean water, for example, is less viscous than mud. The viscosity of blood is directly proportional to resistance and inversely proportional to flow; therefore, any condition that causes viscosity to increase will also increase resistance and decrease flow. For example, imagine sipping milk, then a milkshake, through the same size straw. You experience more resistance and therefore less flow from the milkshake. Conversely, any condition that causes viscosity to decrease (such as when the milkshake melts) will decrease resistance and increase flow.

Normally the viscosity of blood does not change over short periods of time. The two primary determinants of blood viscosity are the formed elements and plasma proteins. Since the vast majority of formed elements are erythrocytes, any condition affecting erythropoiesis, such as polycythemia or anemia, can alter viscosity. Since most plasma proteins are produced by the liver, any condition affecting liver function can also change the viscosity slightly and therefore alter blood flow. Liver abnormalities such as hepatitis, cirrhosis, alcohol damage, and drug toxicities result in decreased levels of plasma proteins, which decrease blood viscosity. While leukocytes and platelets are normally a small component of the formed elements, there are some rare conditions in which severe overproduction can impact viscosity as well.

Vessel Length and Diameter

The length of a vessel is directly proportional to its resistance: the longer the vessel, the greater the resistance and the lower the flow. As with blood volume, this makes intuitive sense, since the increased surface area of the vessel will impede the flow of blood. Likewise, if the vessel is shortened, the resistance will decrease and flow will increase.

The length of our blood vessels increases throughout childhood as we grow, of course, but is unchanging in adults under normal physiological circumstances. Further, the distribution of vessels is not the same in all

tissues. Adipose tissue does not have an extensive vascular supply. One pound of adipose tissue contains approximately 200 miles of vessels, whereas skeletal muscle contains more than twice that. Overall, vessels decrease in length only during loss of mass or amputation. An individual weighing 150 pounds has approximately 60,000 miles of vessels in the body. Gaining about 10 pounds adds from 2000 to 4000 miles of vessels, depending upon the nature of the gained tissue. One of the great benefits of weight reduction is the reduced stress to the heart, which does not have to overcome the resistance of as many miles of vessels.

In contrast to length, the diameter of blood vessels changes throughout the body, according to the type of vessel, as we discussed earlier. The diameter of any given vessel may also change frequently throughout the day in response to neural and chemical signals that trigger vasodilation and vasoconstriction. The **vascular tone** of the vessel is the contractile state of the smooth muscle and the primary determinant of diameter, and thus of resistance and flow. The effect of vessel diameter on resistance is inverse: Given the same volume of blood, an increased diameter means there is less blood contacting the vessel wall, thus lower friction and lower resistance, subsequently increasing flow. A decreased diameter means more of the blood contacts the vessel wall, and resistance increases, subsequently decreasing flow.

The influence of lumen diameter on resistance is dramatic: A slight increase or decrease in diameter causes a huge decrease or increase in resistance. This is because resistance is inversely proportional to the radius of the blood vessel (one-half of the vessel's diameter) raised to the fourth power ($R = 1/r^4$). This means, for example, that if an artery or arteriole constricts to one-half of its original radius, the resistance to flow will increase 16 times. And if an artery or arteriole dilates to twice its initial radius, then resistance in the vessel will decrease to 1/16 of its original value and flow will increase 16 times.

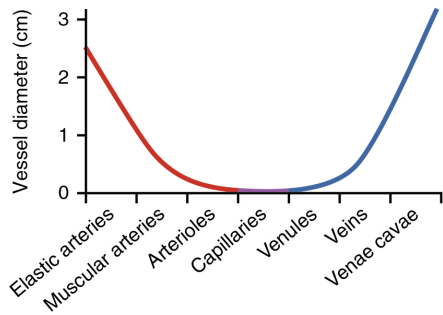
The Roles of Vessel Diameter and Total Area in Blood Flow and Blood Pressure

Recall that we classified arterioles as resistance vessels, because given their small lumen, they dramatically slow the flow of blood from arteries. In fact, arterioles are the site of greatest resistance in the entire vascular network. This may seem surprising, given that capillaries have a smaller size. How can this phenomenon be explained?

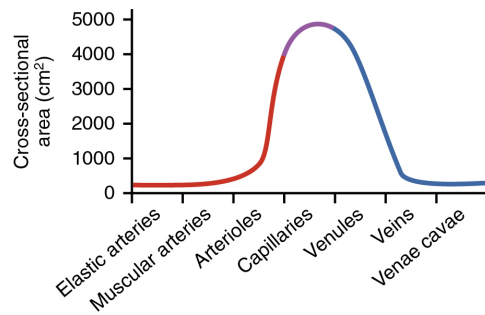
[\[link\]](#) compares vessel diameter, total cross-sectional area, average blood pressure, and blood velocity through the systemic vessels. Notice in parts (a) and (b) that the total cross-sectional area of the body's capillary beds is far greater than any other type of vessel. Although the diameter of an individual capillary is significantly smaller than the diameter of an arteriole, there are vastly more capillaries in the body than there are other types of blood vessels. Part (c) shows that blood pressure drops unevenly as blood travels from arteries to arterioles, capillaries, venules, and veins, and encounters greater resistance. However, the site of the most precipitous drop, and the site of greatest resistance, is the arterioles. This explains why vasodilation and vasoconstriction of arterioles play more significant roles in regulating blood pressure than do the vasodilation and vasoconstriction of other vessels.

Part (d) shows that the velocity (speed) of blood flow decreases dramatically as the blood moves from arteries to arterioles to capillaries. This slow flow rate allows more time for exchange processes to occur. As blood flows through the veins, the rate of velocity increases, as blood is returned to the heart.

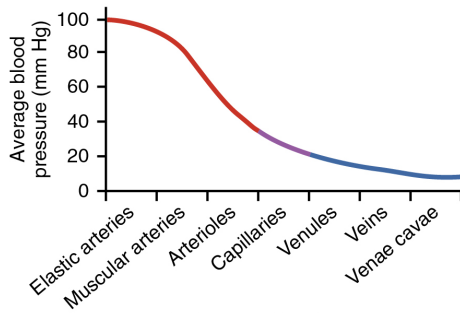
Relationships among Vessels in the Systemic Circuit



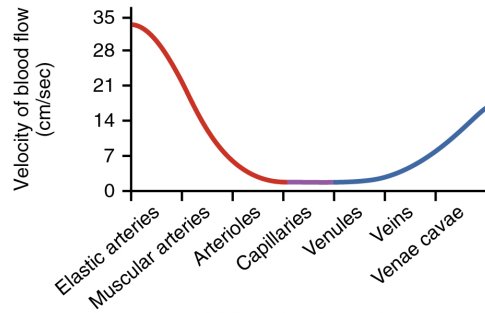
(a) Vessel diameter



(b) Total cross-sectional area of vessels



(c) Average blood pressure



(d) Velocity of blood flow

The relationships among blood vessels that can be compared include (a) vessel diameter, (b) total cross-sectional area, (c) average blood pressure, and (d) velocity of blood flow.

Note:

Disorders of the...

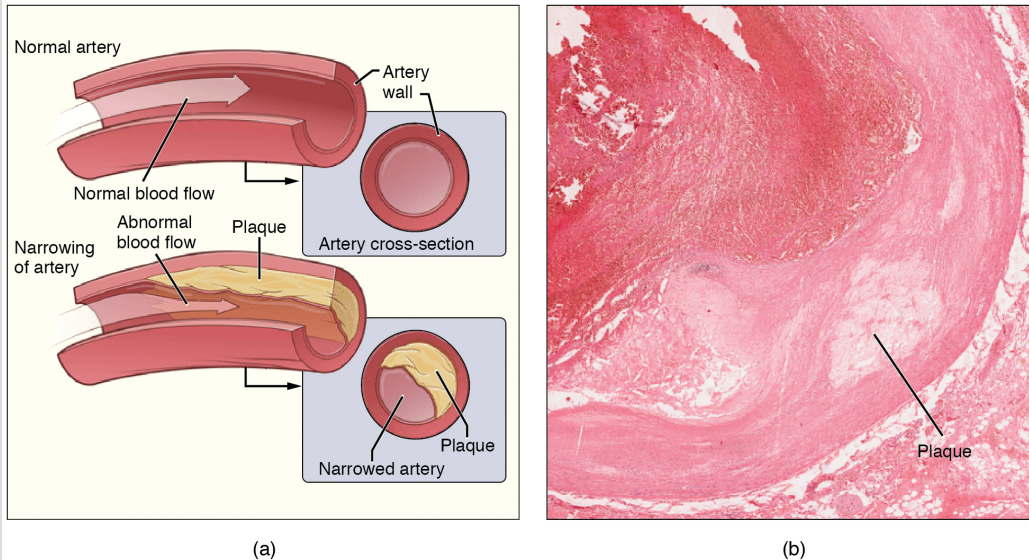
Cardiovascular System: Arteriosclerosis

Compliance allows an artery to expand when blood is pumped through it from the heart, and then to recoil after the surge has passed. This helps promote blood flow. In arteriosclerosis, compliance is reduced, and pressure and resistance within the vessel increase. This is a leading cause of hypertension and coronary heart disease, as it causes the heart to work harder to generate a pressure great enough to overcome the resistance. Arteriosclerosis begins with injury to the endothelium of an artery, which may be caused by irritation from high blood glucose, infection, tobacco use, excessive blood lipids, and other factors. Artery walls that are

constantly stressed by blood flowing at high pressure are also more likely to be injured—which means that hypertension can promote arteriosclerosis, as well as result from it.

Recall that tissue injury causes inflammation. As inflammation spreads into the artery wall, it weakens and scars it, leaving it stiff (sclerotic). As a result, compliance is reduced. Moreover, circulating triglycerides and cholesterol can seep between the damaged lining cells and become trapped within the artery wall, where they are frequently joined by leukocytes, calcium, and cellular debris. Eventually, this buildup, called plaque, can narrow arteries enough to impair blood flow. The term for this condition, atherosclerosis (athero- = “porridge”) describes the mealy deposits ([link](#)).

Atherosclerosis



(a) Atherosclerosis can result from plaques formed by the buildup of fatty, calcified deposits in an artery. (b) Plaques can also take other forms, as shown in this micrograph of a coronary artery that has a buildup of connective tissue within the artery wall. LM $\times 40$. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Sometimes a plaque can rupture, causing microscopic tears in the artery wall that allow blood to leak into the tissue on the other side. When this happens, platelets rush to the site to clot the blood. This clot can further

obstruct the artery and—if it occurs in a coronary or cerebral artery—cause a sudden heart attack or stroke. Alternatively, plaque can break off and travel through the bloodstream as an embolus until it blocks a more distant, smaller artery.

Even without total blockage, vessel narrowing leads to ischemia—reduced blood flow—to the tissue region “downstream” of the narrowed vessel. Ischemia in turn leads to hypoxia—decreased supply of oxygen to the tissues. Hypoxia involving cardiac muscle or brain tissue can lead to cell death and severe impairment of brain or heart function.

A major risk factor for both arteriosclerosis and atherosclerosis is advanced age, as the conditions tend to progress over time. Arteriosclerosis is normally defined as the more generalized loss of compliance, “hardening of the arteries,” whereas atherosclerosis is a more specific term for the build-up of plaque in the walls of the vessel and is a specific type of arteriosclerosis. There is also a distinct genetic component, and pre-existing hypertension and/or diabetes also greatly increase the risk. However, obesity, poor nutrition, lack of physical activity, and tobacco use all are major risk factors.

Treatment includes lifestyle changes, such as weight loss, smoking cessation, regular exercise, and adoption of a diet low in sodium and saturated fats. Medications to reduce cholesterol and blood pressure may be prescribed. For blocked coronary arteries, surgery is warranted. In angioplasty, a catheter is inserted into the vessel at the point of narrowing, and a second catheter with a balloon-like tip is inflated to widen the opening. To prevent subsequent collapse of the vessel, a small mesh tube called a stent is often inserted. In an endarterectomy, plaque is surgically removed from the walls of a vessel. This operation is typically performed on the carotid arteries of the neck, which are a prime source of oxygenated blood for the brain. In a coronary bypass procedure, a non-vital superficial vessel from another part of the body (often the great saphenous vein) or a synthetic vessel is inserted to create a path around the blocked area of a coronary artery.

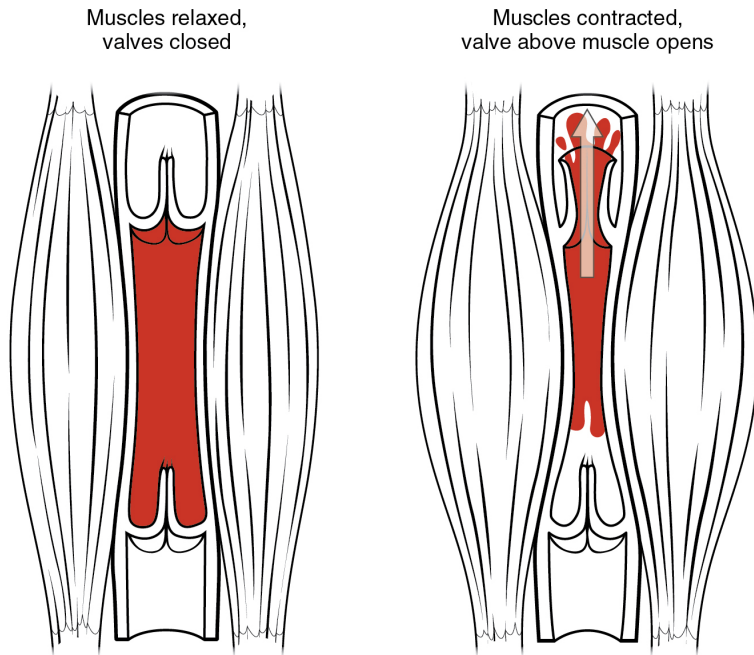
Venous System

The pumping action of the heart propels the blood into the arteries, from an area of higher pressure toward an area of lower pressure. If blood is to flow from the veins back into the heart, the pressure in the veins must be greater than the pressure in the atria of the heart. Two factors help maintain this pressure gradient between the veins and the heart. First, the pressure in the atria during diastole is very low, often approaching zero when the atria are relaxed (atrial diastole). Second, two physiologic “pumps” increase pressure in the venous system. The use of the term “pump” implies a physical device that speeds flow. These physiological pumps are less obvious.

Skeletal Muscle Pump

In many body regions, the pressure within the veins can be increased by the contraction of the surrounding skeletal muscle. This mechanism, known as the **skeletal muscle pump** ([link](#)), helps the lower-pressure veins counteract the force of gravity, increasing pressure to move blood back to the heart. As leg muscles contract, for example during walking or running, they exert pressure on nearby veins with their numerous one-way valves. This increased pressure causes blood to flow upward, opening valves superior to the contracting muscles so blood flows through. Simultaneously, valves inferior to the contracting muscles close; thus, blood should not seep back downward toward the feet. Military recruits are trained to flex their legs slightly while standing at attention for prolonged periods. Failure to do so may allow blood to pool in the lower limbs rather than returning to the heart. Consequently, the brain will not receive enough oxygenated blood, and the individual may lose consciousness.

Skeletal Muscle Pump



The contraction of skeletal muscles surrounding a vein compresses the blood and increases the pressure in that area. This action forces blood closer to the heart where venous pressure is lower. Note the importance of the one-way valves to assure that blood flows only in the proper direction.

Respiratory Pump

The **respiratory pump** aids blood flow through the veins of the thorax and abdomen. During inhalation, the volume of the thorax increases, largely through the contraction of the diaphragm, which moves downward and compresses the abdominal cavity. The elevation of the chest caused by the contraction of the external intercostal muscles also contributes to the increased volume of the thorax. The volume increase causes air pressure within the thorax to decrease, allowing us to inhale. Additionally, as air

pressure within the thorax drops, blood pressure in the thoracic veins also decreases, falling below the pressure in the abdominal veins. This causes blood to flow along its pressure gradient from veins outside the thorax, where pressure is higher, into the thoracic region, where pressure is now lower. This in turn promotes the return of blood from the thoracic veins to the atria. During exhalation, when air pressure increases within the thoracic cavity, pressure in the thoracic veins increases, speeding blood flow into the heart while valves in the veins prevent blood from flowing backward from the thoracic and abdominal veins.

Pressure Relationships in the Venous System

Although vessel diameter increases from the smaller venules to the larger veins and eventually to the venae cavae (singular = vena cava), the total cross-sectional area actually decreases (see [\[link\]](#)a and b). The individual veins are larger in diameter than the venules, but their total number is much lower, so their total cross-sectional area is also lower.

Also notice that, as blood moves from venules to veins, the average blood pressure drops (see [\[link\]](#)c), but the blood velocity actually increases (see [\[link\]](#)). This pressure gradient drives blood back toward the heart. Again, the presence of one-way valves and the skeletal muscle and respiratory pumps contribute to this increased flow. Since approximately 64 percent of the total blood volume resides in systemic veins, any action that increases the flow of blood through the veins will increase venous return to the heart. Maintaining vascular tone within the veins prevents the veins from merely distending, dampening the flow of blood, and as you will see, vasoconstriction actually enhances the flow.

The Role of Venos constriction in Resistance, Blood Pressure, and Flow

As previously discussed, vasoconstriction of an artery or arteriole decreases the radius, increasing resistance and pressure, but decreasing flow. Venos constriction, on the other hand, has a very different outcome. The

walls of veins are thin but irregular; thus, when the smooth muscle in those walls constricts, the lumen becomes more rounded. The more rounded the lumen, the less surface area the blood encounters, and the less resistance the vessel offers. Vasoconstriction increases pressure within a vein as it does in an artery, but in veins, the increased pressure increases flow. Recall that the pressure in the atria, into which the venous blood will flow, is very low, approaching zero for at least part of the relaxation phase of the cardiac cycle. Thus, venoconstriction increases the return of blood to the heart. Another way of stating this is that venoconstriction increases the preload or stretch of the cardiac muscle and increases contraction.

Chapter Review

Blood flow is the movement of blood through a vessel, tissue, or organ. The slowing or blocking of blood flow is called resistance. Blood pressure is the force that blood exerts upon the walls of the blood vessels or chambers of the heart. The components of blood pressure include systolic pressure, which results from ventricular contraction, and diastolic pressure, which results from ventricular relaxation. Pulse pressure is the difference between systolic and diastolic measures, and mean arterial pressure is the “average” pressure of blood in the arterial system, driving blood into the tissues. Pulse, the expansion and recoiling of an artery, reflects the heartbeat. The variables affecting blood flow and blood pressure in the systemic circulation are cardiac output, compliance, blood volume, blood viscosity, and the length and diameter of the blood vessels. In the arterial system, vasodilation and vasoconstriction of the arterioles is a significant factor in systemic blood pressure: Slight vasodilation greatly decreases resistance and increases flow, whereas slight vasoconstriction greatly increases resistance and decreases flow. In the arterial system, as resistance increases, blood pressure increases and flow decreases. In the venous system, constriction increases blood pressure as it does in arteries; the increasing pressure helps to return blood to the heart. In addition, constriction causes the vessel lumen to become more rounded, decreasing resistance and increasing blood flow. Venoconstriction, while less important than arterial vasoconstriction, works with the skeletal muscle pump, the respiratory pump, and their valves to promote venous return to the heart.

Review Questions

Exercise:

Problem:

In a blood pressure measurement of 110/70, the number 70 is the _____.

- a. systolic pressure
- b. diastolic pressure
- c. pulse pressure
- d. mean arterial pressure

Solution:

B

Exercise:

Problem: A healthy elastic artery _____.

- a. is compliant
- b. reduces blood flow
- c. is a resistance artery
- d. has a thin wall and irregular lumen

Solution:

A

Exercise:

Problem: Which of the following statements is *true*?

- a. The longer the vessel, the lower the resistance and the greater the flow.

- b. As blood volume decreases, blood pressure and blood flow also decrease.
 - c. Increased viscosity increases blood flow.
 - d. All of the above are true.
-

Solution:

B

Exercise:

Problem: Slight vasodilation in an arteriole prompts a _____.

- a. slight increase in resistance
 - b. huge increase in resistance
 - c. slight decrease in resistance
 - d. huge decrease in resistance
-

Solution:

D

Exercise:

Problem: Venoconstriction increases which of the following?

- a. blood pressure within the vein
 - b. blood flow within the vein
 - c. return of blood to the heart
 - d. all of the above
-

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

You measure a patient's blood pressure at 130/85. Calculate the patient's pulse pressure and mean arterial pressure. Determine whether each pressure is low, normal, or high.

Solution:

The patient's pulse pressure is $130 - 85 = 45$ mm Hg. Generally, a pulse pressure should be at least 25 percent of the systolic pressure, but not more than 100 mm Hg. Since 25 percent of 130 = 32.5, the patient's pulse pressure of 45 is normal. The patient's mean arterial pressure is $85 + \frac{1}{3}(45) = 85 + 15 = 100$. Normally, the mean arterial blood pressure falls within the range of 70 – 110 mmHg, so 100 is normal.

Exercise:

Problem:

An obese patient comes to the clinic complaining of swollen feet and ankles, fatigue, shortness of breath, and often feeling “spaced out.” She is a cashier in a grocery store, a job that requires her to stand all day. Outside of work, she engages in no physical activity. She confesses that, because of her weight, she finds even walking uncomfortable. Explain how the skeletal muscle pump might play a role in this patient's signs and symptoms.

Solution:

People who stand upright all day and are inactive overall have very little skeletal muscle activity in the legs. Pooling of blood in the legs and feet is common. Venous return to the heart is reduced, a condition that in turn reduces cardiac output and therefore oxygenation of tissues throughout the body. This could at least partially account for the

patient's fatigue and shortness of breath, as well as her "spaced out" feeling, which commonly reflects reduced oxygen to the brain.

Glossary

blood flow

movement of blood through a vessel, tissue, or organ that is usually expressed in terms of volume per unit of time

blood pressure

force exerted by the blood against the wall of a vessel or heart chamber; can be described with the more generic term hydrostatic pressure

compliance

degree to which a blood vessel can stretch as opposed to being rigid

diastolic pressure

lower number recorded when measuring arterial blood pressure; represents the minimal value corresponding to the pressure that remains during ventricular relaxation

hypervolemia

abnormally high levels of fluid and blood within the body

hypovolemia

abnormally low levels of fluid and blood within the body

hypoxia

lack of oxygen supply to the tissues

ischemia

insufficient blood flow to the tissues

Korotkoff sounds

noises created by turbulent blood flow through the vessels

mean arterial pressure (MAP)

average driving force of blood to the tissues; approximated by taking diastolic pressure and adding 1/3 of pulse pressure

pulse

alternating expansion and recoil of an artery as blood moves through the vessel; an indicator of heart rate

pulse pressure

difference between the systolic and diastolic pressures

resistance

any condition or parameter that slows or counteracts the flow of blood

respiratory pump

increase in the volume of the thorax during inhalation that decreases air pressure, enabling venous blood to flow into the thoracic region, then exhalation increases pressure, moving blood into the atria

skeletal muscle pump

effect on increasing blood pressure within veins by compression of the vessel caused by the contraction of nearby skeletal muscle

sphygmomanometer

blood pressure cuff attached to a device that measures blood pressure

systolic pressure

larger number recorded when measuring arterial blood pressure; represents the maximum value following ventricular contraction

vascular tone

contractile state of smooth muscle in a blood vessel

Capillary Exchange

By the end of this section, you will be able to:

- Identify the primary mechanisms of capillary exchange
- Distinguish between capillary hydrostatic pressure and blood colloid osmotic pressure, explaining the contribution of each to net filtration pressure
- Compare filtration and reabsorption
- Explain the fate of fluid that is not reabsorbed from the tissues into the vascular capillaries

The primary purpose of the cardiovascular system is to circulate gases, nutrients, wastes, and other substances to and from the cells of the body. Small molecules, such as gases, lipids, and lipid-soluble molecules, can diffuse directly through the membranes of the endothelial cells of the capillary wall. Glucose, amino acids, and ions—including sodium, potassium, calcium, and chloride—use transporters to move through specific channels in the membrane by facilitated diffusion. Glucose, ions, and larger molecules may also leave the blood through intercellular clefts. Larger molecules can pass through the pores of fenestrated capillaries, and even large plasma proteins can pass through the great gaps in the sinusoids. Some large proteins in blood plasma can move into and out of the endothelial cells packaged within vesicles by endocytosis and exocytosis. Water moves by osmosis.

Bulk Flow

The mass movement of fluids into and out of capillary beds requires a transport mechanism far more efficient than mere diffusion. This movement, often referred to as bulk flow, involves two pressure-driven mechanisms: Volumes of fluid move from an area of higher pressure in a capillary bed to an area of lower pressure in the tissues via **filtration**. In contrast, the movement of fluid from an area of higher pressure in the tissues into an area of lower pressure in the capillaries is **reabsorption**. Two types of pressure interact to drive each of these movements: hydrostatic pressure and osmotic pressure.

Hydrostatic Pressure

The primary force driving fluid transport between the capillaries and tissues is hydrostatic pressure, which can be defined as the pressure of any fluid enclosed in a space. **Blood hydrostatic pressure** is the force exerted by the blood confined within blood vessels or heart chambers. Even more specifically, the pressure exerted by blood against the wall of a capillary is called **capillary hydrostatic pressure (CHP)**, and is the same as capillary blood pressure. CHP is the force that drives fluid out of capillaries and into the tissues.

As fluid exits a capillary and moves into tissues, the hydrostatic pressure in the interstitial fluid correspondingly rises. This opposing hydrostatic pressure is called the **interstitial fluid hydrostatic pressure (IFHP)**. Generally, the CHP originating from the arterial pathways is considerably higher than the IFHP, because lymphatic vessels are continually absorbing excess fluid from the tissues. Thus, fluid generally moves out of the capillary and into the interstitial fluid. This process is called filtration.

Osmotic Pressure

The net pressure that drives reabsorption—the movement of fluid from the interstitial fluid back into the capillaries—is called osmotic pressure (sometimes referred to as oncotic pressure). Whereas hydrostatic pressure forces fluid out of the capillary, osmotic pressure draws fluid back in. Osmotic pressure is determined by osmotic concentration gradients, that is, the difference in the solute-to-water concentrations in the blood and tissue fluid. A region higher in solute concentration (and lower in water concentration) draws water across a semipermeable membrane from a region higher in water concentration (and lower in solute concentration).

As we discuss osmotic pressure in blood and tissue fluid, it is important to recognize that the formed elements of blood do not contribute to osmotic concentration gradients. Rather, it is the plasma proteins that play the key role. Solutes also move across the capillary wall according to their concentration gradient, but overall, the concentrations should be similar and

not have a significant impact on osmosis. Because of their large size and chemical structure, plasma proteins are not truly solutes, that is, they do not dissolve but are dispersed or suspended in their fluid medium, forming a colloid rather than a solution.

The pressure created by the concentration of colloidal proteins in the blood is called the **blood colloidal osmotic pressure (BCOP)**. Its effect on capillary exchange accounts for the reabsorption of water. The plasma proteins suspended in blood cannot move across the semipermeable capillary cell membrane, and so they remain in the plasma. As a result, blood has a higher colloidal concentration and lower water concentration than tissue fluid. It therefore attracts water. We can also say that the BCOP is higher than the **interstitial fluid colloidal osmotic pressure (IFCOP)**, which is always very low because interstitial fluid contains few proteins. Thus, water is drawn from the tissue fluid back into the capillary, carrying dissolved molecules with it. This difference in colloidal osmotic pressure accounts for reabsorption.

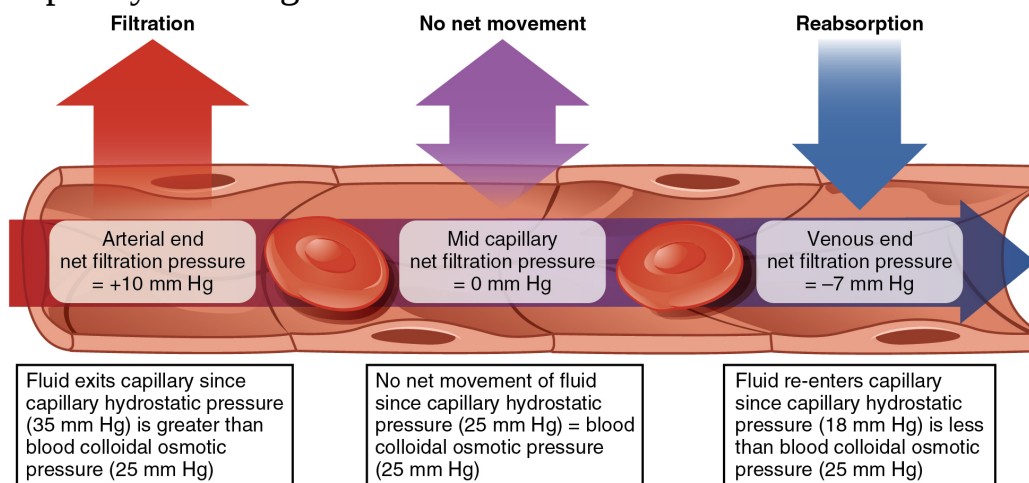
Interaction of Hydrostatic and Osmotic Pressures

The normal unit used to express pressures within the cardiovascular system is millimeters of mercury (mm Hg). When blood leaving an arteriole first enters a capillary bed, the CHP is quite high—about 35 mm Hg. Gradually, this initial CHP declines as the blood moves through the capillary so that by the time the blood has reached the venous end, the CHP has dropped to approximately 18 mm Hg. In comparison, the plasma proteins remain suspended in the blood, so the BCOP remains fairly constant at about 25 mm Hg throughout the length of the capillary and considerably below the osmotic pressure in the interstitial fluid.

The **net filtration pressure (NFP)** represents the interaction of the hydrostatic and osmotic pressures, driving fluid out of the capillary. It is equal to the difference between the CHP and the BCOP. Since filtration is, by definition, the movement of fluid out of the capillary, when reabsorption is occurring, the NFP is a negative number.

NFP changes at different points in a capillary bed ([link](#)). Close to the arterial end of the capillary, it is approximately 10 mm Hg, because the CHP of 35 mm Hg minus the BCOP of 25 mm Hg equals 10 mm Hg. Recall that the hydrostatic and osmotic pressures of the interstitial fluid are essentially negligible. Thus, the NFP of 10 mm Hg drives a net movement of fluid out of the capillary at the arterial end. At approximately the middle of the capillary, the CHP is about the same as the BCOP of 25 mm Hg, so the NFP drops to zero. At this point, there is no net change of volume: Fluid moves out of the capillary at the same rate as it moves into the capillary. Near the venous end of the capillary, the CHP has dwindled to about 18 mm Hg due to loss of fluid. Because the BCOP remains steady at 25 mm Hg, water is drawn into the capillary, that is, reabsorption occurs. Another way of expressing this is to say that at the venous end of the capillary, there is an NFP of -7 mm Hg.

Capillary Exchange



Net filtration occurs near the arterial end of the capillary since capillary hydrostatic pressure (CHP) is greater than blood colloidal osmotic pressure (BCOP). There is no net movement of fluid near the midpoint since $\text{CHP} = \text{BCOP}$. Net reabsorption occurs near the venous end since BCOP is greater than CHP.

The Role of Lymphatic Capillaries

Since overall CHP is higher than BCOP, it is inevitable that more net fluid will exit the capillary through filtration at the arterial end than enters through reabsorption at the venous end. Considering all capillaries over the course of a day, this can be quite a substantial amount of fluid:

Approximately 24 liters per day are filtered, whereas 20.4 liters are reabsorbed. This excess fluid is picked up by capillaries of the lymphatic system. These extremely thin-walled vessels have copious numbers of valves that ensure unidirectional flow through ever-larger lymphatic vessels that eventually drain into the subclavian veins in the neck. An important function of the lymphatic system is to return the fluid (lymph) to the blood. Lymph may be thought of as recycled blood plasma. (Seek additional content for more detail on the lymphatic system.)

Note:



Watch this [video](#) to explore capillaries and how they function in the body. Capillaries are never more than 100 micrometers away. What is the main component of interstitial fluid?

Chapter Review

Small molecules can cross into and out of capillaries via simple or facilitated diffusion. Some large molecules can cross in vesicles or through clefts, fenestrations, or gaps between cells in capillary walls. However, the bulk flow of capillary and tissue fluid occurs via filtration and reabsorption. Filtration, the movement of fluid out of the capillaries, is driven by the CHP. Reabsorption, the influx of tissue fluid into the capillaries, is driven by the BCOP. Filtration predominates in the arterial end of the capillary; in

the middle section, the opposing pressures are virtually identical so there is no net exchange, whereas reabsorption predominates at the venule end of the capillary. The hydrostatic and colloid osmotic pressures in the interstitial fluid are negligible in healthy circumstances.

Interactive Link Questions

Exercise:

Problem:

Watch this [video](#) to explore capillaries and how they function in the body. Capillaries are never more than 100 micrometers away. What is the main component of interstitial fluid?

Solution:

Water.

Review Questions

Exercise:

Problem: Hydrostatic pressure is _____.

- a. greater than colloid osmotic pressure at the venous end of the capillary bed
 - b. the pressure exerted by fluid in an enclosed space
 - c. about zero at the midpoint of a capillary bed
 - d. all of the above
-

Solution:

B

Exercise:

Problem: Net filtration pressure is calculated by _____.

- a. adding the capillary hydrostatic pressure to the interstitial fluid hydrostatic pressure
- b. subtracting the fluid drained by the lymphatic vessels from the total fluid in the interstitial fluid
- c. adding the blood colloid osmotic pressure to the capillary hydrostatic pressure
- d. subtracting the blood colloid osmotic pressure from the capillary hydrostatic pressure

Solution:

D

Exercise:

Problem: Which of the following statements is true?

- a. In one day, more fluid exits the capillary through filtration than enters through reabsorption.
- b. In one day, approximately 35 mm of blood are filtered and 7 mm are reabsorbed.
- c. In one day, the capillaries of the lymphatic system absorb about 20.4 liters of fluid.
- d. None of the above are true.

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

A patient arrives at the emergency department with dangerously low blood pressure. The patient's blood colloid osmotic pressure is normal. How would you expect this situation to affect the patient's net filtration pressure?

Solution:

The patient's blood would flow more sluggishly from the arteriole into the capillary bed. Thus, the patient's capillary hydrostatic pressure would be below the normal 35 mm Hg at the arterial end. At the same time, the patient's blood colloidal osmotic pressure is normal—about 25 mm Hg. Thus, even at the arterial end of the capillary bed, the net filtration pressure would be below 10 mm Hg, and an abnormally reduced level of filtration would occur. In fact, reabsorption might begin to occur by the midpoint of the capillary bed.

Exercise:**Problem:**

True or false? The plasma proteins suspended in blood cross the capillary cell membrane and enter the tissue fluid via facilitated diffusion. Explain your thinking.

Solution:

False. The plasma proteins suspended in blood cannot cross the semipermeable capillary cell membrane, and so they remain in the plasma within the vessel, where they account for the blood colloid osmotic pressure.

Glossary

blood colloidal osmotic pressure (BCOP)

pressure exerted by colloids suspended in blood within a vessel; a primary determinant is the presence of plasma proteins

blood hydrostatic pressure

force blood exerts against the walls of a blood vessel or heart chamber

capillary hydrostatic pressure (CHP)

force blood exerts against a capillary

filtration

in the cardiovascular system, the movement of material from a capillary into the interstitial fluid, moving from an area of higher pressure to lower pressure

interstitial fluid colloidal osmotic pressure (IFCOP)

pressure exerted by the colloids within the interstitial fluid

interstitial fluid hydrostatic pressure (IFHP)

force exerted by the fluid in the tissue spaces

net filtration pressure (NFP)

force driving fluid out of the capillary and into the tissue spaces; equal to the difference of the capillary hydrostatic pressure and the blood colloidal osmotic pressure

reabsorption

in the cardiovascular system, the movement of material from the interstitial fluid into the capillaries

Homeostatic Regulation of the Vascular System

By the end of this section, you will be able to:

- Discuss the mechanisms involved in the neural regulation of vascular homeostasis
- Describe the contribution of a variety of hormones to the renal regulation of blood pressure
- Identify the effects of exercise on vascular homeostasis
- Discuss how hypertension, hemorrhage, and circulatory shock affect vascular health

In order to maintain homeostasis in the cardiovascular system and provide adequate blood to the tissues, blood flow must be redirected continually to the tissues as they become more active. In a very real sense, the cardiovascular system engages in resource allocation, because there is not enough blood flow to distribute blood equally to all tissues simultaneously. For example, when an individual is exercising, more blood will be directed to skeletal muscles, the heart, and the lungs. Following a meal, more blood is directed to the digestive system. Only the brain receives a more or less constant supply of blood whether you are active, resting, thinking, or engaged in any other activity.

[\[link\]](#) provides the distribution of systemic blood at rest and during exercise. Although most of the data appears logical, the values for the distribution of blood to the integument may seem surprising. During exercise, the body distributes more blood to the body surface where it can dissipate the excess heat generated by increased activity into the environment.

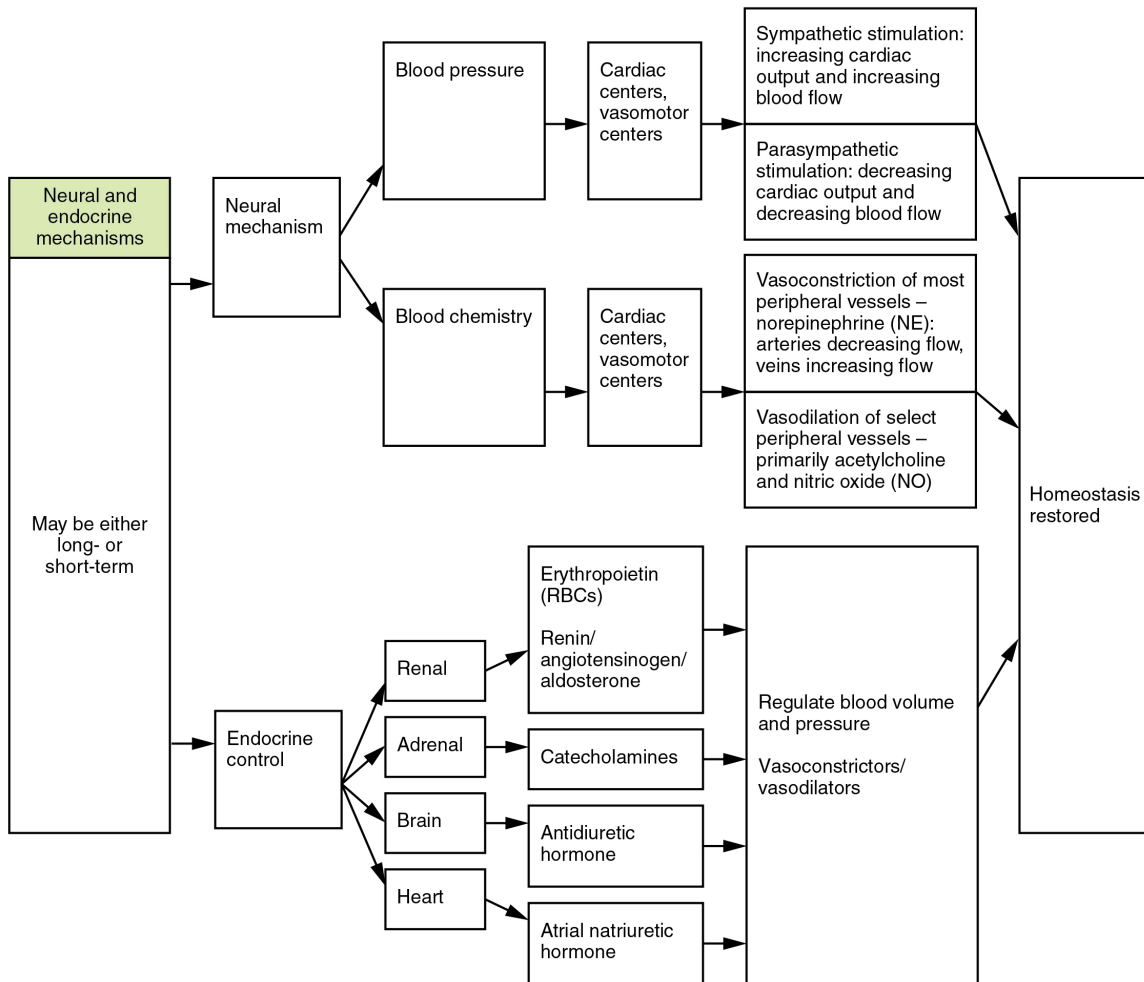
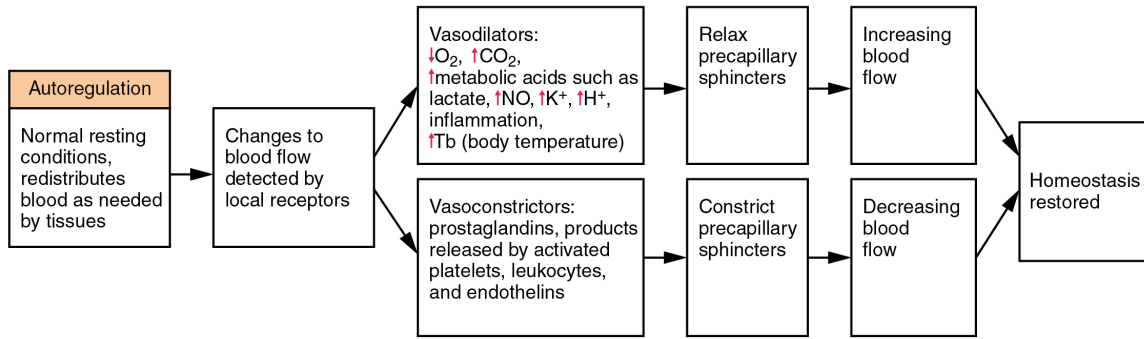
Systemic Blood Flow During Rest, Mild Exercise, and Maximal Exercise in a Healthy Young Individual

| Systemic Blood Flow During Rest, Mild Exercise, and Maximal Exercise in a Healthy Young Individual | | | |
|---|-----------------------------|-----------------------------------|--------------------------------------|
| Organ | Resting (mL/min) | Mild exercise (mL/min) | Maximal exercise (mL/min) |

| Organ | Resting (mL/min) | Mild exercise (mL/min) | Maximal exercise (mL/min) |
|------------------------------------|-----------------------------|-----------------------------------|--------------------------------------|
| Skeletal muscle | 1200 | 4500 | 12,500 |
| Heart | 250 | 350 | 750 |
| Brain | 750 | 750 | 750 |
| Integument | 500 | 1500 | 1900 |
| Kidney | 1100 | 900 | 600 |
| Gastrointestinal | 1400 | 1100 | 600 |
| Others (i.e., liver, spleen) | 600 | 400 | 400 |
| Total | 5800 | 9500 | 17,500 |

Three homeostatic mechanisms ensure adequate blood flow, blood pressure, distribution, and ultimately perfusion: neural, endocrine, and autoregulatory mechanisms. They are summarized in [\[link\]](#).

Summary of Factors Maintaining Vascular Homeostasis



Adequate blood flow, blood pressure, distribution, and perfusion involve autoregulatory, neural, and endocrine mechanisms.

Neural Regulation

The nervous system plays a critical role in the regulation of vascular homeostasis. The primary regulatory sites include the cardiovascular centers in the brain that control both cardiac and vascular functions. In addition, more generalized neural responses from the limbic system and the autonomic nervous system are factors.

The Cardiovascular Centers in the Brain

Neurological regulation of blood pressure and flow depends on the cardiovascular centers located in the medulla oblongata. This cluster of neurons responds to changes in blood pressure as well as blood concentrations of oxygen, carbon dioxide, and hydrogen ions. The cardiovascular center contains three distinct paired components:

- The cardioaccelerator centers stimulate cardiac function by regulating heart rate and stroke volume via sympathetic stimulation from the cardiac accelerator nerve.
- The cardioinhibitor centers slow cardiac function by decreasing heart rate and stroke volume via parasympathetic stimulation from the vagus nerve.
- The vasomotor centers control vessel tone or contraction of the smooth muscle in the tunica media. Changes in diameter affect peripheral resistance, pressure, and flow, which affect cardiac output. The majority of these neurons act via the release of the neurotransmitter norepinephrine from sympathetic neurons.

Although each center functions independently, they are not anatomically distinct.

There is also a small population of neurons that control vasodilation in the vessels of the brain and skeletal muscles by relaxing the smooth muscle fibers in the vessel tunics. Many of these are cholinergic neurons, that is, they release acetylcholine, which in turn stimulates the vessels' endothelial cells to release nitric oxide (NO), which causes vasodilation. Others release

norepinephrine that binds to β_2 receptors. A few neurons release NO directly as a neurotransmitter.

Recall that mild stimulation of the skeletal muscles maintains muscle tone. A similar phenomenon occurs with vascular tone in vessels. As noted earlier, arterioles are normally partially constricted: With maximal stimulation, their radius may be reduced to one-half of the resting state. Full dilation of most arterioles requires that this sympathetic stimulation be suppressed. When it is, an arteriole can expand by as much as 150 percent. Such a significant increase can dramatically affect resistance, pressure, and flow.

Baroreceptor Reflexes

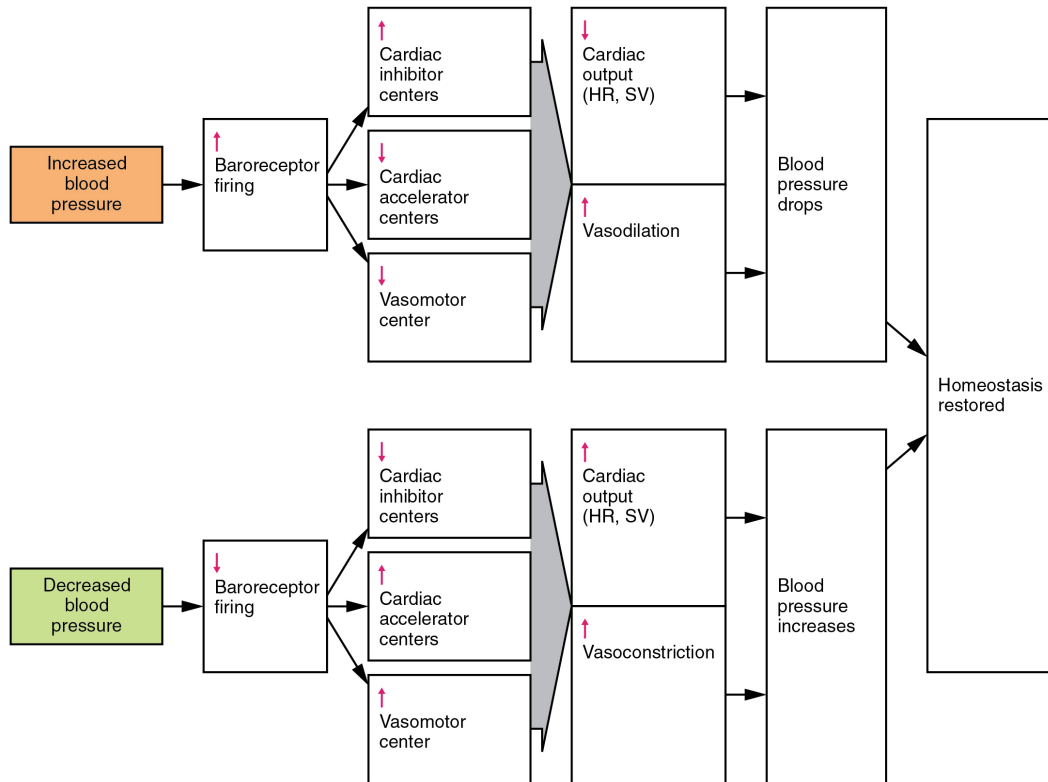
Baroreceptors are specialized stretch receptors located within thin areas of blood vessels and heart chambers that respond to the degree of stretch caused by the presence of blood. They send impulses to the cardiovascular center to regulate blood pressure. Vascular baroreceptors are found primarily in sinuses (small cavities) within the aorta and carotid arteries: The **aortic sinuses** are found in the walls of the ascending aorta just superior to the aortic valve, whereas the **carotid sinuses** are in the base of the internal carotid arteries. There are also low-pressure baroreceptors located in the walls of the venae cavae and right atrium.

When blood pressure increases, the baroreceptors are stretched more tightly and initiate action potentials at a higher rate. At lower blood pressures, the degree of stretch is lower and the rate of firing is slower. When the cardiovascular center in the medulla oblongata receives this input, it triggers a reflex that maintains homeostasis ([\[link\]](#)):

- When blood pressure rises too high, the baroreceptors fire at a higher rate and trigger parasympathetic stimulation of the heart. As a result, cardiac output falls. Sympathetic stimulation of the peripheral arterioles will also decrease, resulting in vasodilation. Combined, these activities cause blood pressure to fall.

- When blood pressure drops too low, the rate of baroreceptor firing decreases. This will trigger an increase in sympathetic stimulation of the heart, causing cardiac output to increase. It will also trigger sympathetic stimulation of the peripheral vessels, resulting in vasoconstriction. Combined, these activities cause blood pressure to rise.

Baroreceptor Reflexes for Maintaining Vascular Homeostasis



Increased blood pressure results in increased rates of baroreceptor firing, whereas decreased blood pressure results in slower rates of fire, both initiating the homeostatic mechanism to restore blood pressure.

The baroreceptors in the venae cavae and right atrium monitor blood pressure as the blood returns to the heart from the systemic circulation. Normally, blood flow into the aorta is the same as blood flow back into the right atrium. If blood is returning to the right atrium more rapidly than it is

being ejected from the left ventricle, the atrial receptors will stimulate the cardiovascular centers to increase sympathetic firing and increase cardiac output until homeostasis is achieved. The opposite is also true. This mechanism is referred to as the **atrial reflex**.

Chemoreceptor Reflexes

In addition to the baroreceptors are chemoreceptors that monitor levels of oxygen, carbon dioxide, and hydrogen ions (pH), and thereby contribute to vascular homeostasis. Chemoreceptors monitoring the blood are located in close proximity to the baroreceptors in the aortic and carotid sinuses. They signal the cardiovascular center as well as the respiratory centers in the medulla oblongata.

Since tissues consume oxygen and produce carbon dioxide and acids as waste products, when the body is more active, oxygen levels fall and carbon dioxide levels rise as cells undergo cellular respiration to meet the energy needs of activities. This causes more hydrogen ions to be produced, causing the blood pH to drop. When the body is resting, oxygen levels are higher, carbon dioxide levels are lower, more hydrogen is bound, and pH rises. (Seek additional content for more detail about pH.)

The chemoreceptors respond to increasing carbon dioxide and hydrogen ion levels (falling pH) by stimulating the cardioaccelerator and vasomotor centers, increasing cardiac output and constricting peripheral vessels. The cardioinhibitor centers are suppressed. With falling carbon dioxide and hydrogen ion levels (increasing pH), the cardioinhibitor centers are stimulated, and the cardioaccelerator and vasomotor centers are suppressed, decreasing cardiac output and causing peripheral vasodilation. In order to maintain adequate supplies of oxygen to the cells and remove waste products such as carbon dioxide, it is essential that the respiratory system respond to changing metabolic demands. In turn, the cardiovascular system will transport these gases to the lungs for exchange, again in accordance with metabolic demands. This interrelationship of cardiovascular and respiratory control cannot be overemphasized.

Other neural mechanisms can also have a significant impact on cardiovascular function. These include the limbic system that links physiological responses to psychological stimuli, as well as generalized sympathetic and parasympathetic stimulation.

Endocrine Regulation

Endocrine control over the cardiovascular system involves the catecholamines, epinephrine and norepinephrine, as well as several hormones that interact with the kidneys in the regulation of blood volume.

Epinephrine and Norepinephrine

The catecholamines epinephrine and norepinephrine are released by the adrenal medulla, and enhance and extend the body's sympathetic or "fight-or-flight" response (see [\[link\]](#)). They increase heart rate and force of contraction, while temporarily constricting blood vessels to organs not essential for flight-or-fight responses and redirecting blood flow to the liver, muscles, and heart.

Antidiuretic Hormone

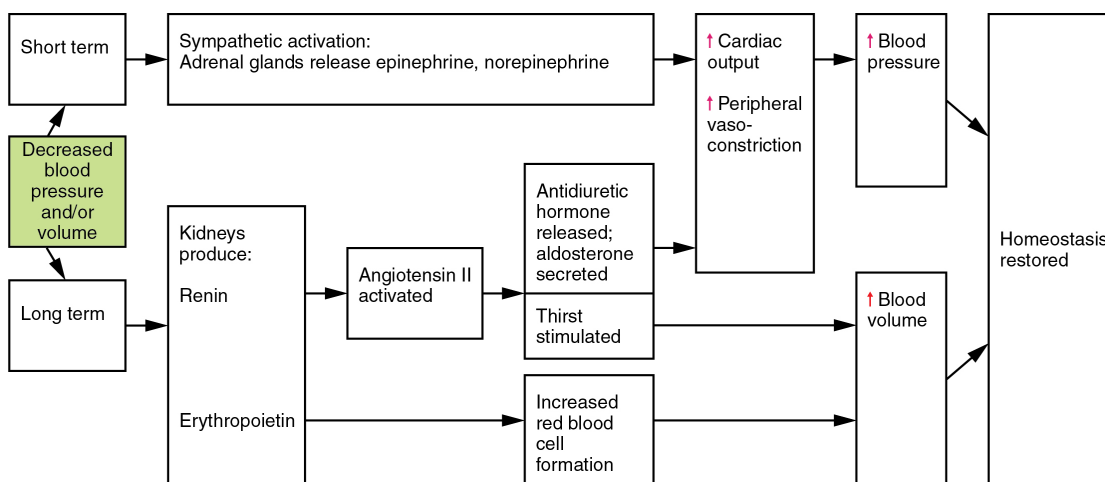
Antidiuretic hormone (ADH), also known as vasopressin, is secreted by the cells in the hypothalamus and transported via the hypothalamic-hypophyseal tracts to the posterior pituitary where it is stored until released upon nervous stimulation. The primary trigger prompting the hypothalamus to release ADH is increasing osmolarity of tissue fluid, usually in response to significant loss of blood volume. ADH signals its target cells in the kidneys to reabsorb more water, thus preventing the loss of additional fluid in the urine. This will increase overall fluid levels and help restore blood volume and pressure. In addition, ADH constricts peripheral vessels.

Renin-Angiotensin-Aldosterone Mechanism

The renin-angiotensin-aldosterone mechanism has a major effect upon the cardiovascular system ([\[link\]](#)). Renin is an enzyme, although because of its importance in the renin-angiotensin-aldosterone pathway, some sources identify it as a hormone. Specialized cells in the kidneys found in the juxtaglomerular apparatus respond to decreased blood flow by secreting renin into the blood. Renin converts the plasma protein angiotensinogen, which is produced by the liver, into its active form—angiotensin I. Angiotensin I circulates in the blood and is then converted into angiotensin II in the lungs. This reaction is catalyzed by the enzyme angiotensin-converting enzyme (ACE).

Angiotensin II is a powerful vasoconstrictor, greatly increasing blood pressure. It also stimulates the release of ADH and aldosterone, a hormone produced by the adrenal cortex. Aldosterone increases the reabsorption of sodium into the blood by the kidneys. Since water follows sodium, this increases the reabsorption of water. This in turn increases blood volume, raising blood pressure. Angiotensin II also stimulates the thirst center in the hypothalamus, so an individual will likely consume more fluids, again increasing blood volume and pressure.

Hormones Involved in Renal Control of Blood Pressure



In the renin-angiotensin-aldosterone mechanism, increasing angiotensin II will stimulate the production of antidiuretic hormone and aldosterone. In addition to renin, the kidneys

produce erythropoietin, which stimulates the production of red blood cells, further increasing blood volume.

Erythropoietin

Erythropoietin (EPO) is released by the kidneys when blood flow and/or oxygen levels decrease. EPO stimulates the production of erythrocytes within the bone marrow. Erythrocytes are the major formed element of the blood and may contribute 40 percent or more to blood volume, a significant factor of viscosity, resistance, pressure, and flow. In addition, EPO is a vasoconstrictor. Overproduction of EPO or excessive intake of synthetic EPO, often to enhance athletic performance, will increase viscosity, resistance, and pressure, and decrease flow in addition to its contribution as a vasoconstrictor.

Atrial Natriuretic Hormone

Secreted by cells in the atria of the heart, atrial natriuretic hormone (ANH) (also known as atrial natriuretic peptide) is secreted when blood volume is high enough to cause extreme stretching of the cardiac cells. Cells in the ventricle produce a hormone with similar effects, called B-type natriuretic hormone. Natriuretic hormones are antagonists to angiotensin II. They promote loss of sodium and water from the kidneys, and suppress renin, aldosterone, and ADH production and release. All of these actions promote loss of fluid from the body, so blood volume and blood pressure drop.

Autoregulation of Perfusion

As the name would suggest, autoregulation mechanisms require neither specialized nervous stimulation nor endocrine control. Rather, these are local, self-regulatory mechanisms that allow each region of tissue to adjust

its blood flow—and thus its perfusion. These local mechanisms include chemical signals and myogenic controls.

Chemical Signals Involved in Autoregulation

Chemical signals work at the level of the precapillary sphincters to trigger either constriction or relaxation. As you know, opening a precapillary sphincter allows blood to flow into that particular capillary, whereas constricting a precapillary sphincter temporarily shuts off blood flow to that region. The factors involved in regulating the precapillary sphincters include the following:

- Opening of the sphincter is triggered in response to decreased oxygen concentrations; increased carbon dioxide concentrations; increasing levels of lactic acid or other byproducts of cellular metabolism; increasing concentrations of potassium ions or hydrogen ions (falling pH); inflammatory chemicals such as histamines; and increased body temperature. These conditions in turn stimulate the release of NO, a powerful vasodilator, from endothelial cells (see [\[link\]](#)).
- Contraction of the precapillary sphincter is triggered by the opposite levels of the regulators, which prompt the release of endothelins, powerful vasoconstricting peptides secreted by endothelial cells. Platelet secretions and certain prostaglandins may also trigger constriction.

Again, these factors alter tissue perfusion via their effects on the precapillary sphincter mechanism, which regulates blood flow to capillaries. Since the amount of blood is limited, not all capillaries can fill at once, so blood flow is allocated based upon the needs and metabolic state of the tissues as reflected in these parameters. Bear in mind, however, that dilation and constriction of the arterioles feeding the capillary beds is the primary control mechanism.

The Myogenic Response

The **myogenic response** is a reaction to the stretching of the smooth muscle in the walls of arterioles as changes in blood flow occur through the vessel. This may be viewed as a largely protective function against dramatic fluctuations in blood pressure and blood flow to maintain homeostasis. If perfusion of an organ is too low (ischemia), the tissue will experience low levels of oxygen (hypoxia). In contrast, excessive perfusion could damage the organ's smaller and more fragile vessels. The myogenic response is a localized process that serves to stabilize blood flow in the capillary network that follows that arteriole.

When blood flow is low, the vessel's smooth muscle will be only minimally stretched. In response, it relaxes, allowing the vessel to dilate and thereby increase the movement of blood into the tissue. When blood flow is too high, the smooth muscle will contract in response to the increased stretch, prompting vasoconstriction that reduces blood flow.

[\[link\]](#) summarizes the effects of nervous, endocrine, and local controls on arterioles.

Summary of Mechanisms Regulating Arteriole Smooth Muscle and Veins

| Control | Factor | Vasoconstriction | Vasodilation |
|---------------|---|--|---|
| Neural | Sympathetic stimulation | Arterioles within integument, abdominal viscera, and mucosa membrane; skeletal muscle (at high levels); varied in veins and venules | Arterioles within heart; skeletal muscles at low to moderate levels |
| | Parasympathetic | No known innervation for most | Arterioles in external genitalia, no known innervation for most other arterioles or veins |
| Endocrine | Epinephrine | Similar to sympathetic stimulation for extended flight-or-fight responses; at high levels, binds to specialized alpha (α) receptors | Similar to sympathetic stimulation for extended fight-or-flight responses; at low to moderate levels, binds to specialized beta (β) receptors |
| | Norepinephrine | Similar to epinephrine | Similar to epinephrine |
| | Angiotensin II | Powerful generalized vasoconstrictor; also stimulates release of aldosterone and ADH | n/a |
| | ANH (peptide) | n/a | Powerful generalized vasodilator; also promotes loss of fluid volume from kidneys, hence reducing blood volume, pressure, and flow |
| | ADH | Moderately strong generalized vasoconstrictor; also causes body to retain more fluid via kidneys, increasing blood volume and pressure | n/a |
| Other factors | Decreasing levels of oxygen | n/a | Vasodilation, also opens precapillary sphincters |
| | Decreasing pH | n/a | Vasodilation, also opens precapillary sphincters |
| | Increasing levels of carbon dioxide | n/a | Vasodilation, also opens precapillary sphincters |
| | Increasing levels of potassium ion | n/a | Vasodilation, also opens precapillary sphincters |
| | Increasing levels of prostaglandins | Vasoconstriction, closes precapillary sphincters for many | Vasodilation, opens precapillary sphincters for many |
| | Increasing levels of adenosine | n/a | Vasodilation |
| | Increasing levels of NO | n/a | Vasodilation, also opens precapillary sphincters |
| | Increasing levels of lactic acid and other metabolites | n/a | Vasodilation, also opens precapillary sphincters |
| | Increasing levels of endothelins | Vasoconstriction | n/a |
| | Increasing levels of platelet secretions | Vasoconstriction | n/a |
| | Increasing hyperthermia | n/a | Vasodilation |
| | Stretching of vascular wall (myogenic) | Vasoconstriction | n/a |
| | Increasing levels of histamines from basophils and mast cells | n/a | Vasodilation |

Effect of Exercise on Vascular Homeostasis

The heart is a muscle and, like any muscle, it responds dramatically to exercise. For a healthy young adult, cardiac output (heart rate \times stroke volume) increases in the nonathlete from approximately 5.0 liters (5.25 quarts) per minute to a maximum of about 20 liters (21 quarts) per minute. Accompanying this will be an increase in blood pressure from about 120/80 to 185/75. However, well-trained aerobic athletes can increase these values

substantially. For these individuals, cardiac output soars from approximately 5.3 liters (5.57 quarts) per minute resting to more than 30 liters (31.5 quarts) per minute during maximal exercise. Along with this increase in cardiac output, blood pressure increases from 120/80 at rest to 200/90 at maximum values.

In addition to improved cardiac function, exercise increases the size and mass of the heart. The average weight of the heart for the nonathlete is about 300 g, whereas in an athlete it will increase to 500 g. This increase in size generally makes the heart stronger and more efficient at pumping blood, increasing both stroke volume and cardiac output.

Tissue perfusion also increases as the body transitions from a resting state to light exercise and eventually to heavy exercise (see [\[link\]](#)). These changes result in selective vasodilation in the skeletal muscles, heart, lungs, liver, and integument. Simultaneously, vasoconstriction occurs in the vessels leading to the kidneys and most of the digestive and reproductive organs. The flow of blood to the brain remains largely unchanged whether at rest or exercising, since the vessels in the brain largely do not respond to regulatory stimuli, in most cases, because they lack the appropriate receptors.

As vasodilation occurs in selected vessels, resistance drops and more blood rushes into the organs they supply. This blood eventually returns to the venous system. Venous return is further enhanced by both the skeletal muscle and respiratory pumps. As blood returns to the heart more quickly, preload rises and the Frank-Starling principle tells us that contraction of the cardiac muscle in the atria and ventricles will be more forceful. Eventually, even the best-trained athletes will fatigue and must undergo a period of rest following exercise. Cardiac output and distribution of blood then return to normal.

Regular exercise promotes cardiovascular health in a variety of ways. Because an athlete's heart is larger than a nonathlete's, stroke volume increases, so the athletic heart can deliver the same amount of blood as the nonathletic heart but with a lower heart rate. This increased efficiency allows the athlete to exercise for longer periods of time before muscles fatigue and places less stress on the heart. Exercise also lowers overall

cholesterol levels by removing from the circulation a complex form of cholesterol, triglycerides, and proteins known as low-density lipoproteins (LDLs), which are widely associated with increased risk of cardiovascular disease. Although there is no way to remove deposits of plaque from the walls of arteries other than specialized surgery, exercise does promote the health of vessels by decreasing the rate of plaque formation and reducing blood pressure, so the heart does not have to generate as much force to overcome resistance.

Generally as little as 30 minutes of noncontinuous exercise over the course of each day has beneficial effects and has been shown to lower the rate of heart attack by nearly 50 percent. While it is always advisable to follow a healthy diet, stop smoking, and lose weight, studies have clearly shown that fit, overweight people may actually be healthier overall than sedentary slender people. Thus, the benefits of moderate exercise are undeniable.

Clinical Considerations in Vascular Homeostasis

Any disorder that affects blood volume, vascular tone, or any other aspect of vascular functioning is likely to affect vascular homeostasis as well. That includes hypertension, hemorrhage, and shock.

Hypertension and Hypotension

Chronically elevated blood pressure is known clinically as **hypertension**. It is defined as chronic and persistent blood pressure measurements of 140/90 mm Hg or above. Pressures between 120/80 and 140/90 mm Hg are defined as prehypertension. About 68 million Americans currently suffer from hypertension. Unfortunately, hypertension is typically a silent disorder; therefore, hypertensive patients may fail to recognize the seriousness of their condition and fail to follow their treatment plan. The result is often a heart attack or stroke. Hypertension may also lead to an aneurism (ballooning of a blood vessel caused by a weakening of the wall), peripheral arterial disease (obstruction of vessels in peripheral regions of the body), chronic kidney disease, or heart failure.

Note:

Listen to this CDC [podcast](#) to learn about hypertension, often described as a “silent killer.” What steps can you take to reduce your risk of a heart attack or stroke?

Hemorrhage

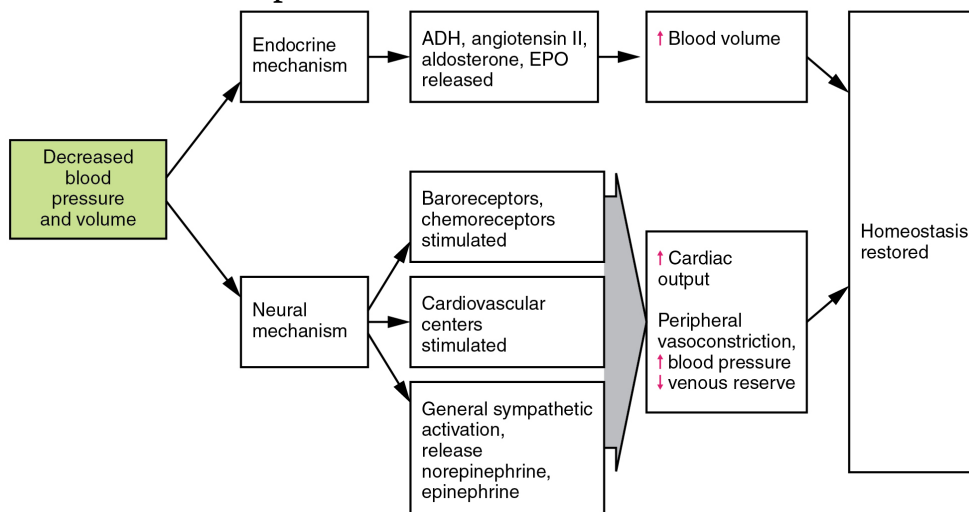
Minor blood loss is managed by hemostasis and repair. Hemorrhage is a loss of blood that cannot be controlled by hemostatic mechanisms. Initially, the body responds to hemorrhage by initiating mechanisms aimed at increasing blood pressure and maintaining blood flow. Ultimately, however, blood volume will need to be restored, either through physiological processes or through medical intervention.

In response to blood loss, stimuli from the baroreceptors trigger the cardiovascular centers to stimulate sympathetic responses to increase cardiac output and vasoconstriction. This typically prompts the heart rate to increase to about 180–200 contractions per minute, restoring cardiac output to normal levels. Vasoconstriction of the arterioles increases vascular resistance, whereas constriction of the veins increases venous return to the heart. Both of these steps will help increase blood pressure. Sympathetic stimulation also triggers the release of epinephrine and norepinephrine, which enhance both cardiac output and vasoconstriction. If blood loss were less than 20 percent of total blood volume, these responses together would usually return blood pressure to normal and redirect the remaining blood to the tissues.

Additional endocrine involvement is necessary, however, to restore the lost blood volume. The angiotensin-renin-aldosterone mechanism stimulates the

thirst center in the hypothalamus, which increases fluid consumption to help restore the lost blood. More importantly, it increases renal reabsorption of sodium and water, reducing water loss in urine output. The kidneys also increase the production of EPO, stimulating the formation of erythrocytes that not only deliver oxygen to the tissues but also increase overall blood volume. [\[link\]](#) summarizes the responses to loss of blood volume.

Homeostatic Responses to Loss of Blood Volume



Circulatory Shock

The loss of too much blood may lead to **circulatory shock**, a life-threatening condition in which the circulatory system is unable to maintain blood flow to adequately supply sufficient oxygen and other nutrients to the tissues to maintain cellular metabolism. It should not be confused with emotional or psychological shock. Typically, the patient in circulatory shock will demonstrate an increased heart rate but decreased blood pressure, but there are cases in which blood pressure will remain normal. Urine output will fall dramatically, and the patient may appear confused or lose consciousness. Urine output less than 1 mL/kg body weight/hour is cause for concern. Unfortunately, shock is an example of a positive-feedback loop that, if uncorrected, may lead to the death of the patient.

There are several recognized forms of shock:

- **Hypovolemic shock** in adults is typically caused by hemorrhage, although in children it may be caused by fluid losses related to severe vomiting or diarrhea. Other causes for hypovolemic shock include extensive burns, exposure to some toxins, and excessive urine loss related to diabetes insipidus or ketoacidosis. Typically, patients present with a rapid, almost tachycardic heart rate; a weak pulse often described as “thread;” cool, clammy skin, particularly in the extremities, due to restricted peripheral blood flow; rapid, shallow breathing; hypothermia; thirst; and dry mouth. Treatments generally involve providing intravenous fluids to restore the patient to normal function and various drugs such as dopamine, epinephrine, and norepinephrine to raise blood pressure.
- **Cardiogenic shock** results from the inability of the heart to maintain cardiac output. Most often, it results from a myocardial infarction (heart attack), but it may also be caused by arrhythmias, valve disorders, cardiomyopathies, cardiac failure, or simply insufficient flow of blood through the cardiac vessels. Treatment involves repairing the damage to the heart or its vessels to resolve the underlying cause, rather than treating cardiogenic shock directly.
- **Vascular shock** occurs when arterioles lose their normal muscular tone and dilate dramatically. It may arise from a variety of causes, and treatments almost always involve fluid replacement and medications, called inotropic or pressor agents, which restore tone to the muscles of the vessels. In addition, eliminating or at least alleviating the underlying cause of the condition is required. This might include antibiotics and antihistamines, or select steroids, which may aid in the repair of nerve damage. A common cause is **sepsis** (or septicemia), also called “blood poisoning,” which is a widespread bacterial infection that results in an organismal-level inflammatory response known as **septic shock**. **Neurogenic shock** is a form of vascular shock that occurs with cranial or spinal injuries that damage the cardiovascular centers in the medulla oblongata or the nervous fibers originating from this region. **Anaphylactic shock** is a severe allergic response that causes the widespread release of histamines, triggering vasodilation throughout the body.
- **Obstructive shock**, as the name would suggest, occurs when a significant portion of the vascular system is blocked. It is not always

recognized as a distinct condition and may be grouped with cardiogenic shock, including pulmonary embolism and cardiac tamponade. Treatments depend upon the underlying cause and, in addition to administering fluids intravenously, often include the administration of anticoagulants, removal of fluid from the pericardial cavity, or air from the thoracic cavity, and surgery as required. The most common cause is a pulmonary embolism, a clot that lodges in the pulmonary vessels and interrupts blood flow. Other causes include stenosis of the aortic valve; cardiac tamponade, in which excess fluid in the pericardial cavity interferes with the ability of the heart to fully relax and fill with blood (resulting in decreased preload); and a pneumothorax, in which an excessive amount of air is present in the thoracic cavity, outside of the lungs, which interferes with venous return, pulmonary function, and delivery of oxygen to the tissues.

Chapter Review

Neural, endocrine, and autoregulatory mechanisms affect blood flow, blood pressure, and eventually perfusion of blood to body tissues. Neural mechanisms include the cardiovascular centers in the medulla oblongata, baroreceptors in the aorta and carotid arteries and right atrium, and associated chemoreceptors that monitor blood levels of oxygen, carbon dioxide, and hydrogen ions. Endocrine controls include epinephrine and norepinephrine, as well as ADH, the renin-angiotensin-aldosterone mechanism, ANH, and EPO. Autoregulation is the local control of vasodilation and constriction by chemical signals and the myogenic response. Exercise greatly improves cardiovascular function and reduces the risk of cardiovascular diseases, including hypertension, a leading cause of heart attacks and strokes. Significant hemorrhage can lead to a form of circulatory shock known as hypovolemic shock. Sepsis, obstruction, and widespread inflammation can also cause circulatory shock.

Interactive Link Questions

Exercise:

Problem:

Listen to this CDC [podcast](#) to learn about hypertension, often described as a “silent killer.” What steps can you take to reduce your risk of a heart attack or stroke?

Solution:

Take medications as prescribed, eat a healthy diet, exercise, and don't smoke.

Review Questions**Exercise:****Problem:**

Clusters of neurons in the medulla oblongata that regulate blood pressure are known collectively as _____.

- a. baroreceptors
 - b. angioreceptors
 - c. the cardiomotor mechanism
 - d. the cardiovascular center
-

Solution:

D

Exercise:

Problem: In the renin-angiotensin-aldosterone mechanism, _____.

- a. decreased blood pressure prompts the release of renin from the liver
- b. aldosterone prompts increased urine output
- c. aldosterone prompts the kidneys to reabsorb sodium

d. all of the above

Solution:

C

Exercise:

Problem:In the myogenic response, _____.

- a. muscle contraction promotes venous return to the heart
- b. ventricular contraction strength is decreased
- c. vascular smooth muscle responds to stretch
- d. endothelins dilate muscular arteries

Solution:

C

Exercise:

Problem:

A form of circulatory shock common in young children with severe diarrhea or vomiting is _____.

- a. hypovolemic shock
- b. anaphylactic shock
- c. obstructive shock
- d. hemorrhagic shock

Solution:

A

Critical Thinking Questions

Exercise:**Problem:**

A patient arrives in the emergency department with a blood pressure of 70/45 confused and complaining of thirst. Why?

Solution:

This blood pressure is insufficient to circulate blood throughout the patient's body and maintain adequate perfusion of the patient's tissues. Ischemia would prompt hypoxia, including to the brain, prompting confusion. The low blood pressure would also trigger the renin-angiotensin-aldosterone mechanism, and release of aldosterone would stimulate the thirst mechanism in the hypothalamus.

Exercise:**Problem:**

Nitric oxide is broken down very quickly after its release. Why?

Solution:

Nitric oxide is a very powerful local vasodilator that is important in the autoregulation of tissue perfusion. If it were not broken down very quickly after its release, blood flow to the region could exceed metabolic needs.

References

Centers for Disease Control and Prevention (US). Getting blood pressure under control: high blood pressure is out of control for too many Americans [Internet]. Atlanta (GA); [cited 2013 Apr 26]. Available from: <http://www.cdc.gov/features/vitalsigns/hypertension/>

Glossary

anaphylactic shock

type of shock that follows a severe allergic reaction and results from massive vasodilation

aortic sinuses

small pockets in the ascending aorta near the aortic valve that are the locations of the baroreceptors (stretch receptors) and chemoreceptors that trigger a reflex that aids in the regulation of vascular homeostasis

atrial reflex

mechanism for maintaining vascular homeostasis involving atrial baroreceptors: if blood is returning to the right atrium more rapidly than it is being ejected from the left ventricle, the atrial receptors will stimulate the cardiovascular centers to increase sympathetic firing and increase cardiac output until the situation is reversed; the opposite is also true

cardiogenic shock

type of shock that results from the inability of the heart to maintain cardiac output

carotid sinuses

small pockets near the base of the internal carotid arteries that are the locations of the baroreceptors and chemoreceptors that trigger a reflex that aids in the regulation of vascular homeostasis

circulatory shock

also simply called shock; a life-threatening medical condition in which the circulatory system is unable to supply enough blood flow to provide adequate oxygen and other nutrients to the tissues to maintain cellular metabolism

hypertension

chronic and persistent blood pressure measurements of 140/90 mm Hg or above

hypovolemic shock

type of circulatory shock caused by excessive loss of blood volume due to hemorrhage or possibly dehydration

myogenic response

constriction or dilation in the walls of arterioles in response to pressures related to blood flow; reduces high blood flow or increases low blood flow to help maintain consistent flow to the capillary network

neurogenic shock

type of shock that occurs with cranial or high spinal injuries that damage the cardiovascular centers in the medulla oblongata or the nervous fibers originating from this region

obstructive shock

type of shock that occurs when a significant portion of the vascular system is blocked

sepsis

(also, septicemia) organismal-level inflammatory response to a massive infection

septic shock

(also, blood poisoning) type of shock that follows a massive infection resulting in organism-wide inflammation

vascular shock

type of shock that occurs when arterioles lose their normal muscular tone and dilate dramatically


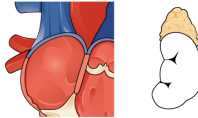


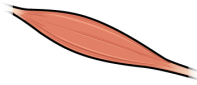




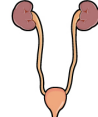
Circulatory Pathways

By the end of this section, you will be able to:

- Identify the vessels through which blood travels within the pulmonary circuit, beginning from the right ventricle of the heart and ending at the left atrium
- Create a flow chart showing the major systemic arteries through which blood travels from the aorta and its major branches, to the most significant arteries feeding into the right and left upper and lower limbs
- Create a flow chart showing the major systemic veins through which blood travels from the feet to the right atrium of the heart

Virtually every cell, tissue, organ, and system in the body is impacted by the circulatory system. This includes the generalized and more specialized functions of transport of materials, capillary exchange, maintaining health by transporting white blood cells and various immunoglobulins (antibodies), hemostasis, regulation of body temperature, and helping to maintain acid-base balance. In addition to these shared functions, many systems enjoy a unique relationship with the circulatory system. [\[link\]](#) summarizes these relationships.

Interaction of the Circulatory System with Other Body Systems

| System | Role of Circulatory System |
|--|--|
| Digestive  | Absorbs nutrients and water; delivers nutrients (except most lipids) to liver for processing by hepatic portal vein; provides nutrients essential for hematopoiesis and building hemoglobin |
| Endocrine  | Delivers hormones: atrial natriuretic hormone (peptide) secreted by the heart atrial cells to help regulate blood volumes and pressures; epinephrine, ANH, angiotensin II, ADH, and thyroxine to help regulate blood pressure; estrogen to promote vascular health in women and men |
| Integumentary  | Carries clotting factors, platelets, and white blood cells for hemostasis, fighting infection, and repairing damage; regulates temperature by controlling blood flow to the surface, where heat can be dissipated; provides some coloration of integument; acts as a blood reservoir |
| Lymphatic  | Transports various white blood cells, including those produced by lymphatic tissue, and immunoglobulins (antibodies) throughout the body to maintain health; carries excess tissue fluid not able to be reabsorbed by the vascular capillaries back to the lymphatic system for processing |
| Muscular  | Provides nutrients and oxygen for contraction; removes lactic acid and distributes heat generated by contraction; muscular pumps aid in venous return; exercise contributes to cardiovascular health and helps to prevent atherosclerosis |
| Nervous  | Produces cerebrospinal fluid (CSF) within choroid plexuses; contributes to blood-brain barrier; cardiac and vasomotor centers regulate cardiac output and blood flow through vessels via autonomic system |
| Reproductive  | Aids in erection of genitalia in both sexes during sexual arousal; transports gonadotropic hormones that regulate reproductive functions |
| Respiratory  | Provides blood for critical exchange of gases to carry oxygen needed for metabolic reactions and carbon dioxide generated as byproducts of these processes |
| Skeletal  | Provides calcium, phosphate, and other minerals critical for bone matrix; transports hormones regulating buildup and absorption of matrix including growth hormone (somatotropin), thyroid hormone, calcitonins, and parathyroid hormone; erythropoietin stimulates myeloid cell hematopoiesis; some level of protection for select vessels by bony structures |
| Urinary  | Delivers 20% of resting circulation to kidneys for filtering, reabsorption of useful products, and secretion of excesses; regulates blood volume and pressure by regulating fluid loss in the form of urine and by releasing the enzyme renin that is essential in the renin-angiotensin-aldosterone mechanism |

As you learn about the vessels of the systemic and pulmonary circuits, notice that many arteries and veins share the same names, parallel one another throughout the body, and are very similar on the right and left sides of the body. These pairs of vessels will be traced through only one side of the body. Where differences occur in branching patterns or when vessels are singular, this will be indicated. For example, you will find a pair of femoral arteries and a pair of femoral veins, with one vessel on each side of the body. In contrast, some vessels closer to the midline of the body, such as the aorta, are unique. Moreover, some superficial veins, such as the great

saphenous vein in the femoral region, have no arterial counterpart. Another phenomenon that can make the study of vessels challenging is that names of vessels can change with location. Like a street that changes name as it passes through an intersection, an artery or vein can change names as it passes an anatomical landmark. For example, the left subclavian artery becomes the axillary artery as it passes through the body wall and into the axillary region, and then becomes the brachial artery as it flows from the axillary region into the upper arm (or brachium). You will also find examples of anastomoses where two blood vessels that previously branched reconnect. Anastomoses are especially common in veins, where they help maintain blood flow even when one vessel is blocked or narrowed, although there are some important ones in the arteries supplying the brain.

As you read about circular pathways, notice that there is an occasional, very large artery referred to as a **trunk**, a term indicating that the vessel gives rise to several smaller arteries. For example, the celiac trunk gives rise to the left gastric, common hepatic, and splenic arteries.

As you study this section, imagine you are on a “Voyage of Discovery” similar to Lewis and Clark’s expedition in 1804–1806, which followed rivers and streams through unfamiliar territory, seeking a water route from the Atlantic to the Pacific Ocean. You might envision being inside a miniature boat, exploring the various branches of the circulatory system. This simple approach has proven effective for many students in mastering these major circulatory patterns. Another approach that works well for many students is to create simple line drawings similar to the ones provided, labeling each of the major vessels. It is beyond the scope of this text to name every vessel in the body. However, we will attempt to discuss the major pathways for blood and acquaint you with the major named arteries and veins in the body. Also, please keep in mind that individual variations in circulation patterns are not uncommon.

Note:



Visit this [site](#) for a brief summary of the arteries.

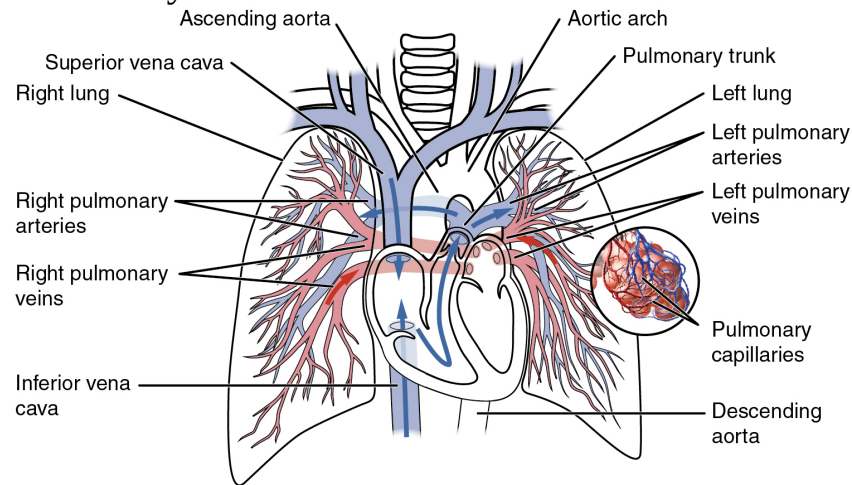
Pulmonary Circulation

Recall that blood returning from the systemic circuit enters the right atrium ([link](#)) via the superior and inferior venae cavae and the coronary sinus, which drains the blood supply of the heart muscle. These vessels will be described more fully later in this section. This blood is relatively low in oxygen and relatively high in carbon dioxide, since much of the oxygen has been extracted for use by the tissues and the waste gas carbon dioxide was picked up to be transported to the lungs for elimination. From the right atrium, blood moves into the right ventricle, which pumps it to the lungs for gas exchange. This system of vessels is referred to as the **pulmonary circuit**.

The single vessel exiting the right ventricle is the **pulmonary trunk**. At the base of the pulmonary trunk is the pulmonary semilunar valve, which prevents backflow of blood into the right ventricle during ventricular diastole. As the pulmonary trunk reaches the superior surface of the heart, it curves posteriorly and rapidly bifurcates (divides) into two branches, a left and a right **pulmonary artery**. To prevent confusion between these vessels, it is important to refer to the vessel exiting the heart as the pulmonary trunk, rather than also calling it a pulmonary artery. The pulmonary arteries in turn branch many times within the lung, forming a series of smaller arteries and arterioles that eventually lead to the pulmonary capillaries. The pulmonary capillaries surround lung structures known as alveoli that are the sites of oxygen and carbon dioxide exchange.

Once gas exchange is completed, oxygenated blood flows from the pulmonary capillaries into a series of pulmonary venules that eventually lead to a series of larger **pulmonary veins**. Four pulmonary veins, two on the left and two on the right, return blood to the left atrium. At this point, the pulmonary circuit is complete. [\[link\]](#) defines the major arteries and veins of the pulmonary circuit discussed in the text.

Pulmonary Circuit



Blood exiting from the right ventricle flows into the pulmonary trunk, which bifurcates into the two pulmonary arteries. These vessels branch to supply blood to the pulmonary capillaries, where gas exchange occurs within the lung alveoli. Blood returns via the pulmonary veins to the left atrium.

Pulmonary Arteries and Veins

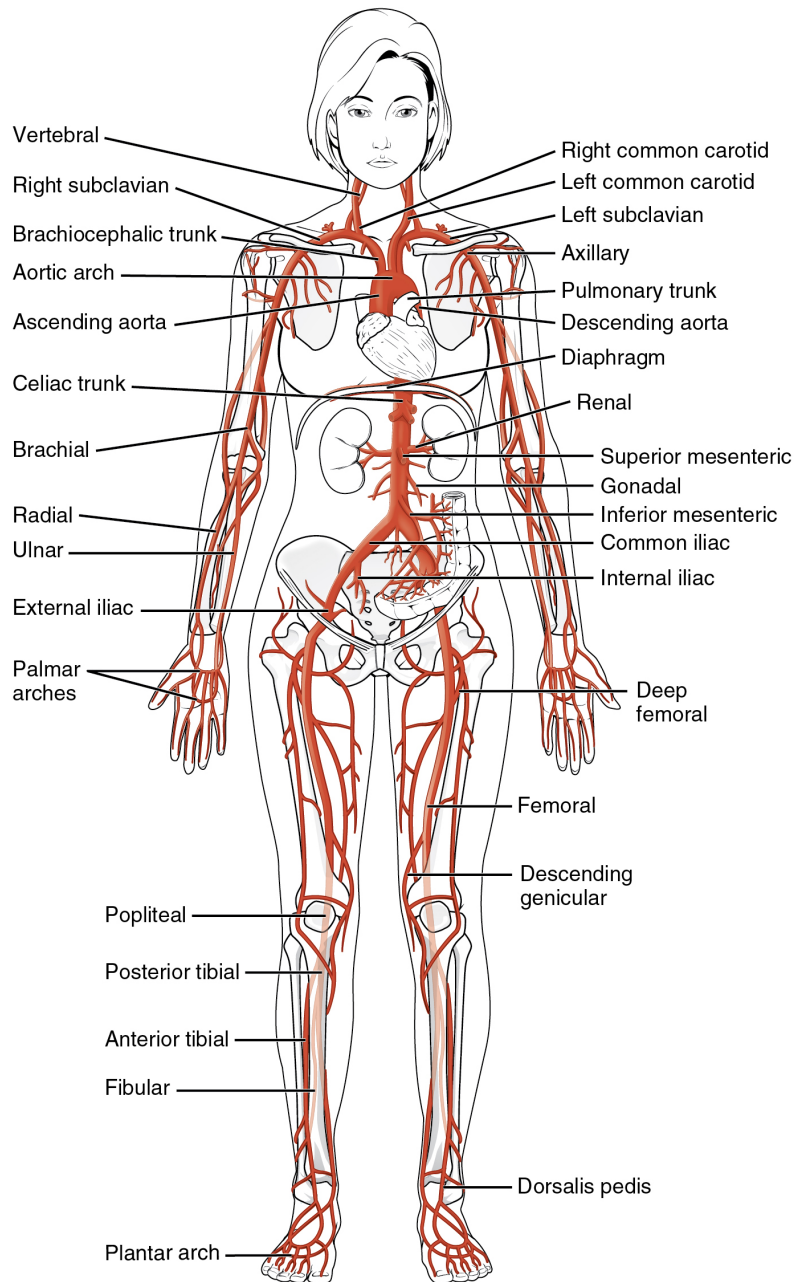
| Vessel | Description |
|--------|-------------|
|--------|-------------|

| Pulmonary Arteries and Veins | |
|-------------------------------------|---|
| Vessel | Description |
| Pulmonary trunk | Single large vessel exiting the right ventricle that divides to form the right and left pulmonary arteries |
| Pulmonary arteries | Left and right vessels that form from the pulmonary trunk and lead to smaller arterioles and eventually to the pulmonary capillaries |
| Pulmonary veins | Two sets of paired vessels—one pair on each side—that are formed from the small venules, leading away from the pulmonary capillaries to flow into the left atrium |

Overview of Systemic Arteries

Blood relatively high in oxygen concentration is returned from the pulmonary circuit to the left atrium via the four pulmonary veins. From the left atrium, blood moves into the left ventricle, which pumps blood into the aorta. The aorta and its branches—the systemic arteries—send blood to virtually every organ of the body ([\[link\]](#)).

Systemic Arteries

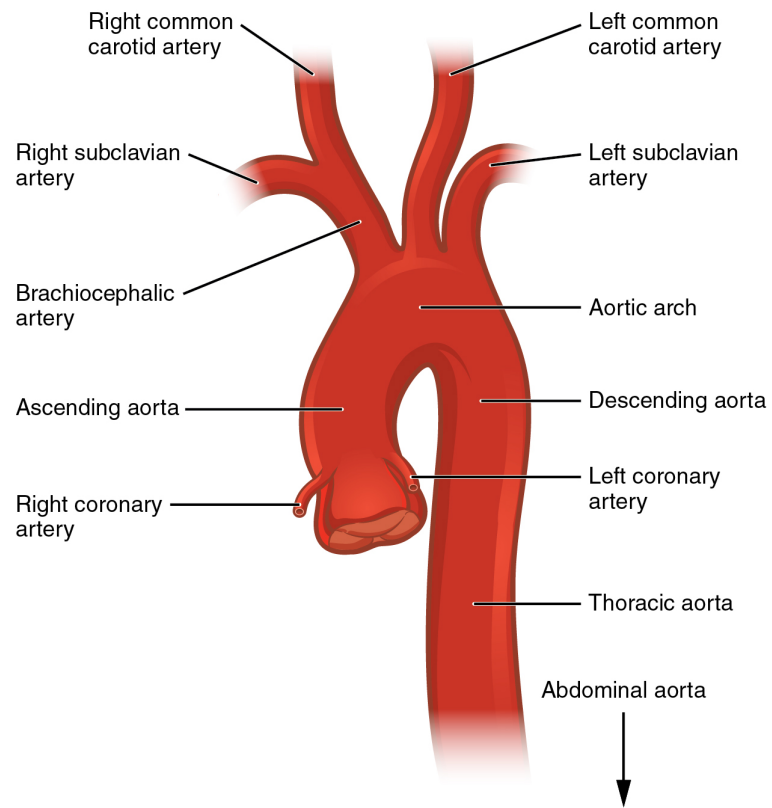


The major systemic arteries shown here deliver oxygenated blood throughout the body.

The Aorta

The **aorta** is the largest artery in the body ([\[link\]](#)). It arises from the left ventricle and eventually descends to the abdominal region, where it bifurcates at the level of the fourth lumbar vertebra into the two common iliac arteries. The aorta consists of the ascending aorta, the aortic arch, and the descending aorta, which passes through the diaphragm and a landmark that divides into the superior thoracic and inferior abdominal components. Arteries originating from the aorta ultimately distribute blood to virtually all tissues of the body. At the base of the aorta is the aortic semilunar valve that prevents backflow of blood into the left ventricle while the heart is relaxing. After exiting the heart, the **ascending aorta** moves in a superior direction for approximately 5 cm and ends at the sternal angle. Following this ascent, it reverses direction, forming a graceful arc to the left, called the **aortic arch**. The aortic arch descends toward the inferior portions of the body and ends at the level of the intervertebral disk between the fourth and fifth thoracic vertebrae. Beyond this point, the **descending aorta** continues close to the bodies of the vertebrae and passes through an opening in the diaphragm known as the **aortic hiatus**. Superior to the diaphragm, the aorta is called the **thoracic aorta**, and inferior to the diaphragm, it is called the **abdominal aorta**. The abdominal aorta terminates when it bifurcates into the two common iliac arteries at the level of the fourth lumbar vertebra. See [\[link\]](#) for an illustration of the ascending aorta, the aortic arch, and the initial segment of the descending aorta plus major branches; [\[link\]](#) summarizes the structures of the aorta.

Aorta



The aorta has distinct regions, including the ascending aorta, aortic arch, and the descending aorta, which includes the thoracic and abdominal regions.

| Components of the Aorta | |
|-------------------------|-------------|
| Vessel | Description |

| Components of the Aorta | |
|--------------------------------|--|
| Vessel | Description |
| Aorta | Largest artery in the body, originating from the left ventricle and descending to the abdominal region, where it bifurcates into the common iliac arteries at the level of the fourth lumbar vertebra; arteries originating from the aorta distribute blood to virtually all tissues of the body |
| Ascending aorta | Initial portion of the aorta, rising superiorly from the left ventricle for a distance of approximately 5 cm |
| Aortic arch | Graceful arc to the left that connects the ascending aorta to the descending aorta; ends at the intervertebral disk between the fourth and fifth thoracic vertebrae |
| Descending aorta | Portion of the aorta that continues inferiorly past the end of the aortic arch; subdivided into the thoracic aorta and the abdominal aorta |
| Thoracic aorta | Portion of the descending aorta superior to the aortic hiatus |
| Abdominal aorta | Portion of the aorta inferior to the aortic hiatus and superior to the common iliac arteries |

Coronary Circulation

The first vessels that branch from the ascending aorta are the paired coronary arteries (see [\[link\]](#)), which arise from two of the three sinuses in the ascending aorta just superior to the aortic semilunar valve. These sinuses contain the aortic baroreceptors and chemoreceptors critical to

maintain cardiac function. The left coronary artery arises from the left posterior aortic sinus. The right coronary artery arises from the anterior aortic sinus. Normally, the right posterior aortic sinus does not give rise to a vessel.

The coronary arteries encircle the heart, forming a ring-like structure that divides into the next level of branches that supplies blood to the heart tissues. (Seek additional content for more detail on cardiac circulation.)

Aortic Arch Branches

There are three major branches of the aortic arch: the brachiocephalic artery, the left common carotid artery, and the left subclavian (literally “under the clavicle”) artery. As you would expect based upon proximity to the heart, each of these vessels is classified as an elastic artery.

The brachiocephalic artery is located only on the right side of the body; there is no corresponding artery on the left. The brachiocephalic artery branches into the right subclavian artery and the right common carotid artery. The left subclavian and left common carotid arteries arise independently from the aortic arch but otherwise follow a similar pattern and distribution to the corresponding arteries on the right side (see [\[link\]](#)).

Each **subclavian artery** supplies blood to the arms, chest, shoulders, back, and central nervous system. It then gives rise to three major branches: the internal thoracic artery, the vertebral artery, and the thyrocervical artery. The **internal thoracic artery**, or mammary artery, supplies blood to the thymus, the pericardium of the heart, and the anterior chest wall. The **vertebral artery** passes through the vertebral foramen in the cervical vertebrae and then through the foramen magnum into the cranial cavity to supply blood to the brain and spinal cord. The paired vertebral arteries join together to form the large basilar artery at the base of the medulla oblongata. This is an example of an anastomosis. The subclavian artery also gives rise to the **thyrocervical artery** that provides blood to the thyroid, the cervical region of the neck, and the upper back and shoulder.

The **common carotid artery** divides into internal and external carotid arteries. The right common carotid artery arises from the brachiocephalic artery and the left common carotid artery arises directly from the aortic arch. The **external carotid artery** supplies blood to numerous structures within the face, lower jaw, neck, esophagus, and larynx. These branches include the lingual, facial, occipital, maxillary, and superficial temporal arteries. The **internal carotid artery** initially forms an expansion known as the carotid sinus, containing the carotid baroreceptors and chemoreceptors. Like their counterparts in the aortic sinuses, the information provided by these receptors is critical to maintaining cardiovascular homeostasis (see [\[link\]](#)).

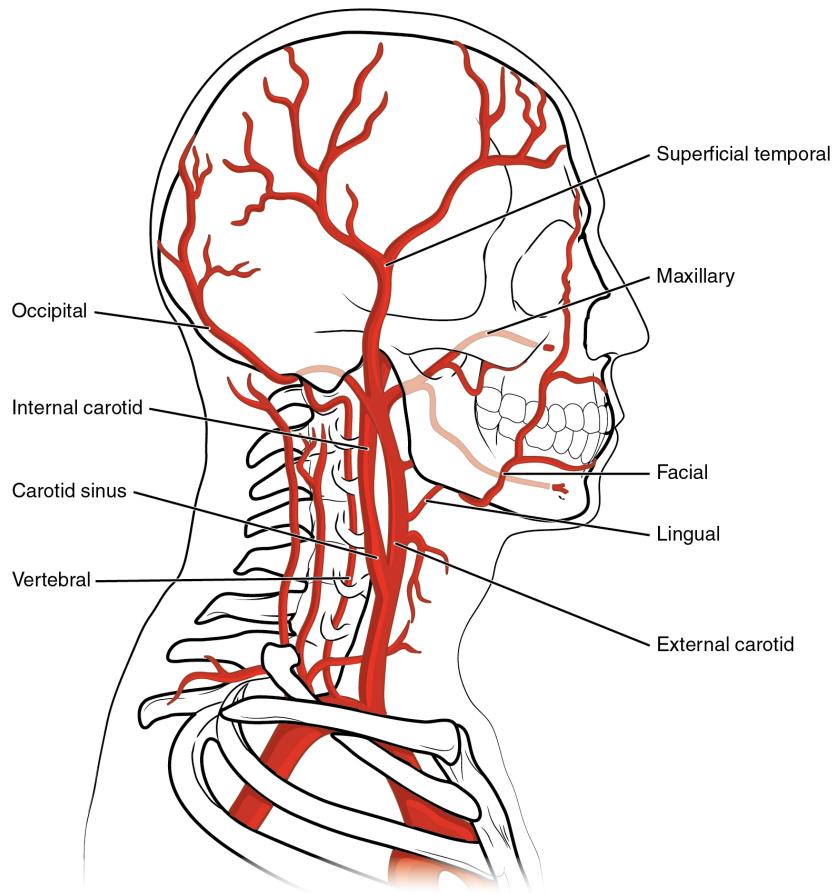
The internal carotid arteries along with the vertebral arteries are the two primary suppliers of blood to the human brain. Given the central role and vital importance of the brain to life, it is critical that blood supply to this organ remains uninterrupted. Recall that blood flow to the brain is remarkably constant, with approximately 20 percent of blood flow directed to this organ at any given time. When blood flow is interrupted, even for just a few seconds, a **transient ischemic attack (TIA)**, or mini-stroke, may occur, resulting in loss of consciousness or temporary loss of neurological function. In some cases, the damage may be permanent. Loss of blood flow for longer periods, typically between 3 and 4 minutes, will likely produce irreversible brain damage or a stroke, also called a **cerebrovascular accident (CVA)**. The locations of the arteries in the brain not only provide blood flow to the brain tissue but also prevent interruption in the flow of blood. Both the carotid and vertebral arteries branch once they enter the cranial cavity, and some of these branches form a structure known as the **arterial circle (or circle of Willis)**, an anastomosis that is remarkably like a traffic circle that sends off branches (in this case, arterial branches to the brain). As a rule, branches to the anterior portion of the cerebrum are normally fed by the internal carotid arteries; the remainder of the brain receives blood flow from branches associated with the vertebral arteries.

The internal carotid artery continues through the carotid canal of the temporal bone and enters the base of the brain through the carotid foramen where it gives rise to several branches ([\[link\]](#) and [\[link\]](#)). One of these branches is the **anterior cerebral artery** that supplies blood to the frontal

lobe of the cerebrum. Another branch, the **middle cerebral artery**, supplies blood to the temporal and parietal lobes, which are the most common sites of CVAs. The **ophthalmic artery**, the third major branch, provides blood to the eyes.

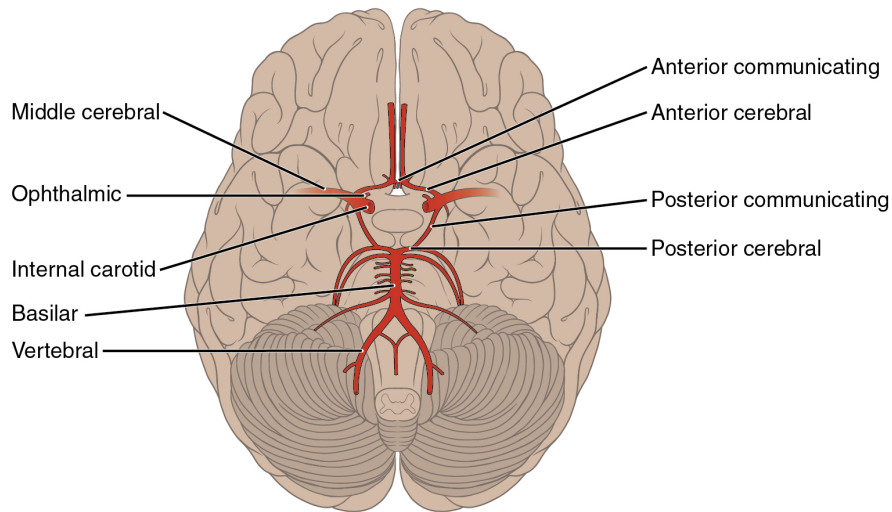
The right and left anterior cerebral arteries join together to form an anastomosis called the **anterior communicating artery**. The initial segments of the anterior cerebral arteries and the anterior communicating artery form the anterior portion of the arterial circle. The posterior portion of the arterial circle is formed by a left and a right **posterior communicating artery** that branches from the **posterior cerebral artery**, which arises from the basilar artery. It provides blood to the posterior portion of the cerebrum and brain stem. The **basilar artery** is an anastomosis that begins at the junction of the two vertebral arteries and sends branches to the cerebellum and brain stem. It flows into the posterior cerebral arteries. [\[link\]](#) summarizes the aortic arch branches, including the major branches supplying the brain.

Arteries Supplying the Head and Neck



The common carotid artery gives rise to the external and internal carotid arteries. The external carotid artery remains superficial and gives rise to many arteries of the head. The internal carotid artery first forms the carotid sinus and then reaches the brain via the carotid canal and carotid foramen, emerging into the cranium via the foramen lacerum. The vertebral artery branches from the subclavian artery and passes through the transverse foramen in the cervical vertebrae, entering the base of the skull at the vertebral foramen. The subclavian artery continues toward the arm as the axillary artery.

Arteries Serving the Brain



This inferior view shows the network of arteries serving the brain. The structure is referred to as the arterial circle or circle of Willis.

| Aortic Arch Branches and Brain Circulation | |
|--|--|
| Vessel | Description |
| Brachiocephalic artery | Single vessel located on the right side of the body; the first vessel branching from the aortic arch; gives rise to the right subclavian artery and the right common carotid artery; supplies blood to the head, neck, upper limb, and wall of the thoracic region |

| Aortic Arch Branches and Brain Circulation | |
|---|---|
| Vessel | Description |
| Subclavian artery | The right subclavian artery arises from the brachiocephalic artery while the left subclavian artery arises from the aortic arch; gives rise to the internal thoracic, vertebral, and thyrocervical arteries; supplies blood to the arms, chest, shoulders, back, and central nervous system |
| Internal thoracic artery | Also called the mammary artery; arises from the subclavian artery; supplies blood to the thymus, pericardium of the heart, and anterior chest wall |
| Vertebral artery | Arises from the subclavian artery and passes through the vertebral foramen through the foramen magnum to the brain; joins with the internal carotid artery to form the arterial circle; supplies blood to the brain and spinal cord |
| Thyrocervical artery | Arises from the subclavian artery; supplies blood to the thyroid, the cervical region, the upper back, and shoulder |
| Common carotid artery | The right common carotid artery arises from the brachiocephalic artery and the left common carotid artery arises from the aortic arch; each gives rise to the external and internal carotid arteries; supplies the respective sides of the head and neck |
| External carotid artery | Arises from the common carotid artery; supplies blood to numerous structures within the face, lower jaw, neck, esophagus, and larynx |

| Aortic Arch Branches and Brain Circulation | |
|---|---|
| Vessel | Description |
| Internal carotid artery | Arises from the common carotid artery and begins with the carotid sinus; goes through the carotid canal of the temporal bone to the base of the brain; combines with the branches of the vertebral artery, forming the arterial circle; supplies blood to the brain |
| Arterial circle or circle of Willis | An anastomosis located at the base of the brain that ensures continual blood supply; formed from the branches of the internal carotid and vertebral arteries; supplies blood to the brain |
| Anterior cerebral artery | Arises from the internal carotid artery; supplies blood to the frontal lobe of the cerebrum |
| Middle cerebral artery | Another branch of the internal carotid artery; supplies blood to the temporal and parietal lobes of the cerebrum |
| Ophthalmic artery | Branch of the internal carotid artery; supplies blood to the eyes |
| Anterior communicating artery | An anastomosis of the right and left internal carotid arteries; supplies blood to the brain |
| Posterior communicating artery | Branches of the posterior cerebral artery that form part of the posterior portion of the arterial circle; supplies blood to the brain |

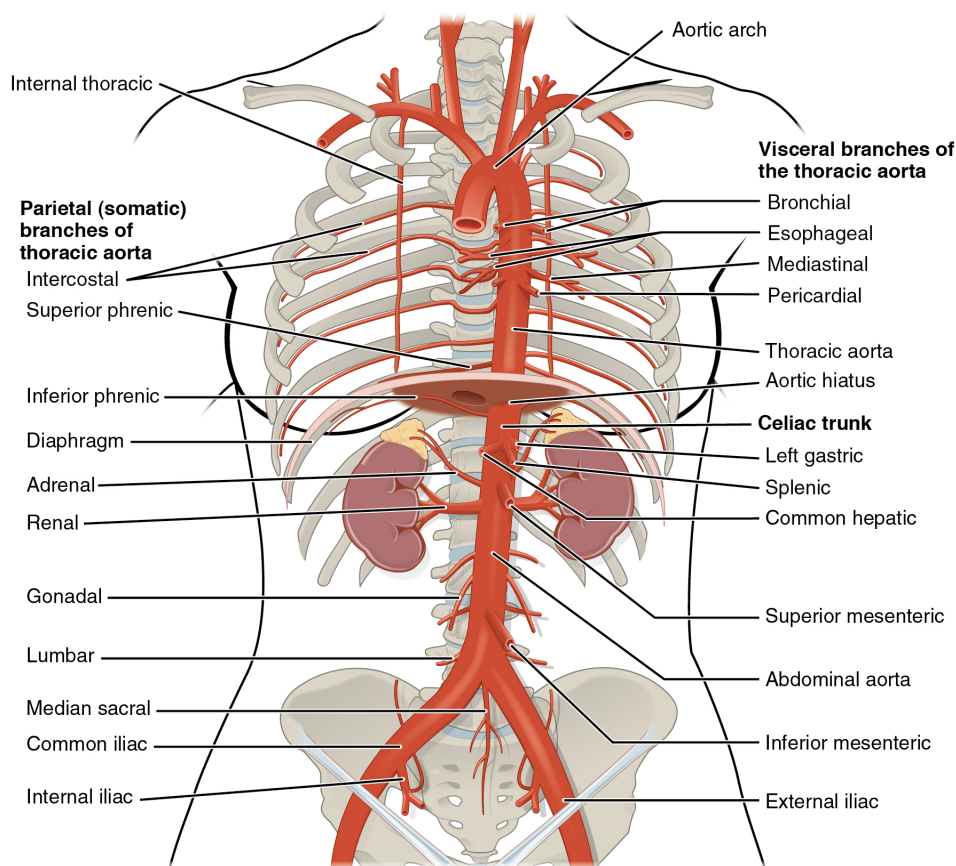
| Aortic Arch Branches and Brain Circulation | |
|--|---|
| Vessel | Description |
| Posterior cerebral artery | Branch of the basilar artery that forms a portion of the posterior segment of the arterial circle of Willis; supplies blood to the posterior portion of the cerebrum and brain stem |
| Basilar artery | Formed from the fusion of the two vertebral arteries; sends branches to the cerebellum, brain stem, and the posterior cerebral arteries; the main blood supply to the brain stem |

Thoracic Aorta and Major Branches

The thoracic aorta begins at the level of vertebra T5 and continues through to the diaphragm at the level of T12, initially traveling within the mediastinum to the left of the vertebral column. As it passes through the thoracic region, the thoracic aorta gives rise to several branches, which are collectively referred to as visceral branches and parietal branches ([\[link\]](#)). Those branches that supply blood primarily to visceral organs are known as the **visceral branches** and include the bronchial arteries, pericardial arteries, esophageal arteries, and the mediastinal arteries, each named after the tissues it supplies. Each **bronchial artery** (typically two on the left and one on the right) supplies systemic blood to the lungs and visceral pleura, in addition to the blood pumped to the lungs for oxygenation via the pulmonary circuit. The bronchial arteries follow the same path as the respiratory branches, beginning with the bronchi and ending with the bronchioles. There is considerable, but not total, intermingling of the systemic and pulmonary blood at anastomoses in the smaller branches of the lungs. This may sound incongruous—that is, the mixing of systemic arterial blood high in oxygen with the pulmonary arterial blood lower in oxygen—but the systemic vessels also deliver nutrients to the lung tissue just as they do elsewhere in the body. The mixed blood drains into typical

pulmonary veins, whereas the bronchial artery branches remain separate and drain into bronchial veins described later. Each **pericardial artery** supplies blood to the pericardium, the **esophageal artery** provides blood to the esophagus, and the **mediastinal artery** provides blood to the mediastinum. The remaining thoracic aorta branches are collectively referred to as **parietal branches** or somatic branches, and include the intercostal and superior phrenic arteries. Each **intercostal artery** provides blood to the muscles of the thoracic cavity and vertebral column. The **superior phrenic artery** provides blood to the superior surface of the diaphragm. [\[link\]](#) lists the arteries of the thoracic region.

Arteries of the Thoracic and Abdominal Regions



The thoracic aorta gives rise to the arteries of the visceral and parietal branches.

| Arteries of the Thoracic Region | |
|--|---|
| Vessel | Description |
| Visceral branches | A group of arterial branches of the thoracic aorta; supplies blood to the viscera (i.e., organs) of the thorax |
| Bronchial artery | Systemic branch from the aorta that provides oxygenated blood to the lungs; this blood supply is in addition to the pulmonary circuit that brings blood for oxygenation |
| Pericardial artery | Branch of the thoracic aorta; supplies blood to the pericardium |
| Esophageal artery | Branch of the thoracic aorta; supplies blood to the esophagus |
| Mediastinal artery | Branch of the thoracic aorta; supplies blood to the mediastinum |
| Parietal branches | Also called somatic branches, a group of arterial branches of the thoracic aorta; include those that supply blood to the thoracic wall, vertebral column, and the superior surface of the diaphragm |
| Intercostal artery | Branch of the thoracic aorta; supplies blood to the muscles of the thoracic cavity and vertebral column |
| Superior phrenic artery | Branch of the thoracic aorta; supplies blood to the superior surface of the diaphragm |

Abdominal Aorta and Major Branches

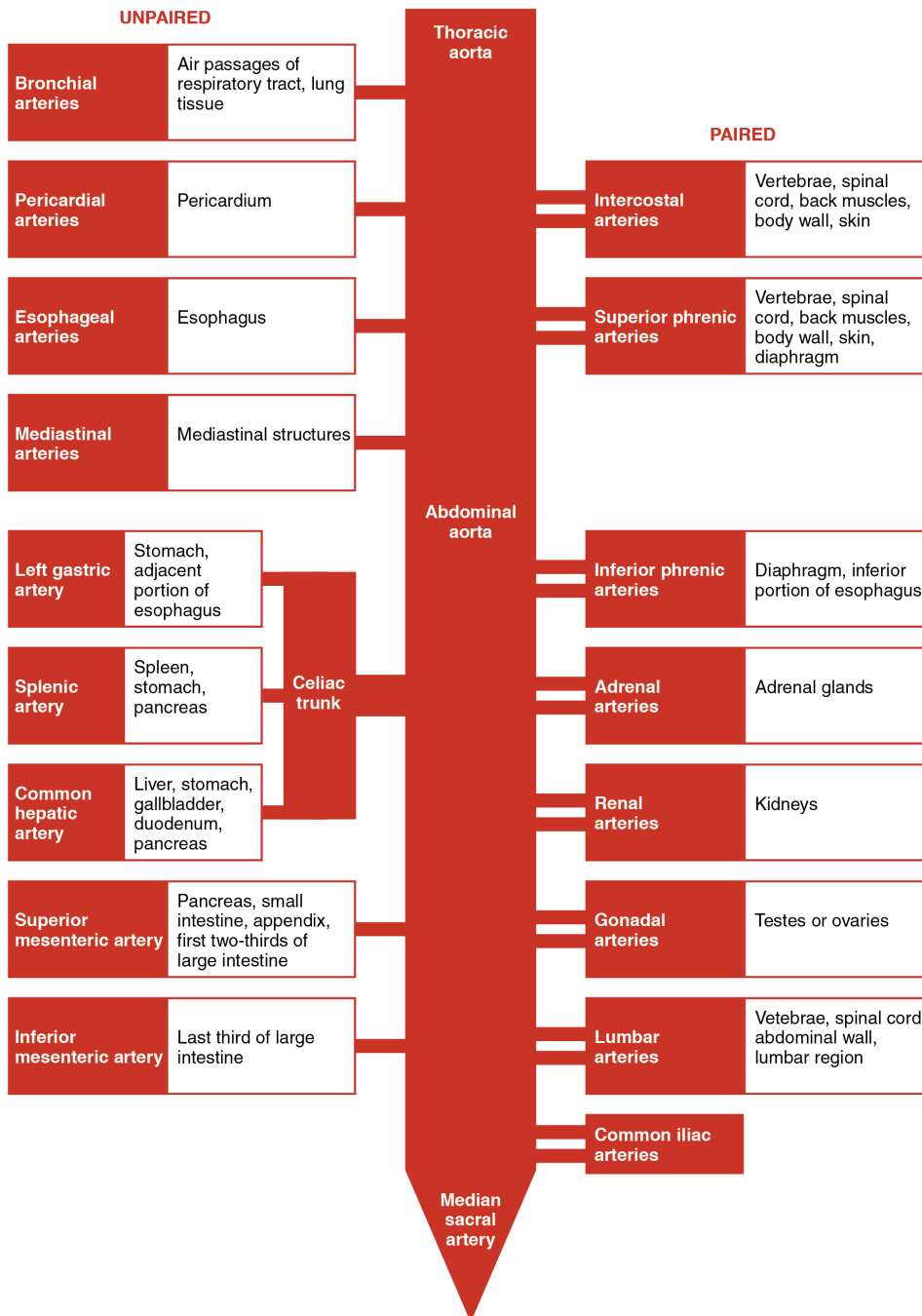
After crossing through the diaphragm at the aortic hiatus, the thoracic aorta is called the abdominal aorta (see [\[link\]](#)). This vessel remains to the left of the vertebral column and is embedded in adipose tissue behind the peritoneal cavity. It formally ends at approximately the level of vertebra L4, where it bifurcates to form the common iliac arteries. Before this division, the abdominal aorta gives rise to several important branches. A single **celiac trunk** (artery) emerges and divides into the **left gastric artery** to supply blood to the stomach and esophagus, the **splenic artery** to supply blood to the spleen, and the **common hepatic artery**, which in turn gives rise to the **hepatic artery proper** to supply blood to the liver, the **right gastric artery** to supply blood to the stomach, the **cystic artery** to supply blood to the gall bladder, and several branches, one to supply blood to the duodenum and another to supply blood to the pancreas. Two additional single vessels arise from the abdominal aorta. These are the superior and inferior mesenteric arteries. The **superior mesenteric artery** arises approximately 2.5 cm after the celiac trunk and branches into several major vessels that supply blood to the small intestine (duodenum, jejunum, and ileum), the pancreas, and a majority of the large intestine. The **inferior mesenteric artery** supplies blood to the distal segment of the large intestine, including the rectum. It arises approximately 5 cm superior to the common iliac arteries.

In addition to these single branches, the abdominal aorta gives rise to several significant paired arteries along the way. These include the inferior phrenic arteries, the adrenal arteries, the renal arteries, the gonadal arteries, and the lumbar arteries. Each **inferior phrenic artery** is a counterpart of a superior phrenic artery and supplies blood to the inferior surface of the diaphragm. The **adrenal artery** supplies blood to the adrenal (suprarenal) glands and arises near the superior mesenteric artery. Each **renal artery** branches approximately 2.5 cm inferior to the superior mesenteric arteries and supplies a kidney. The right renal artery is longer than the left since the aorta lies to the left of the vertebral column and the vessel must travel a greater distance to reach its target. Renal arteries branch repeatedly to supply blood to the kidneys. Each **gonadal artery** supplies blood to the gonads, or reproductive organs, and is also described as either an ovarian

artery or a testicular artery (internal spermatic), depending upon the sex of the individual. An **ovarian artery** supplies blood to an ovary, uterine (Fallopian) tube, and the uterus, and is located within the suspensory ligament of the uterus. It is considerably shorter than a **testicular artery**, which ultimately travels outside the body cavity to the testes, forming one component of the spermatic cord. The gonadal arteries arise inferior to the renal arteries and are generally retroperitoneal. The ovarian artery continues to the uterus where it forms an anastomosis with the uterine artery that supplies blood to the uterus. Both the uterine arteries and vaginal arteries, which distribute blood to the vagina, are branches of the internal iliac artery. The four paired **lumbar arteries** are the counterparts of the intercostal arteries and supply blood to the lumbar region, the abdominal wall, and the spinal cord. In some instances, a fifth pair of lumbar arteries emerges from the median sacral artery.

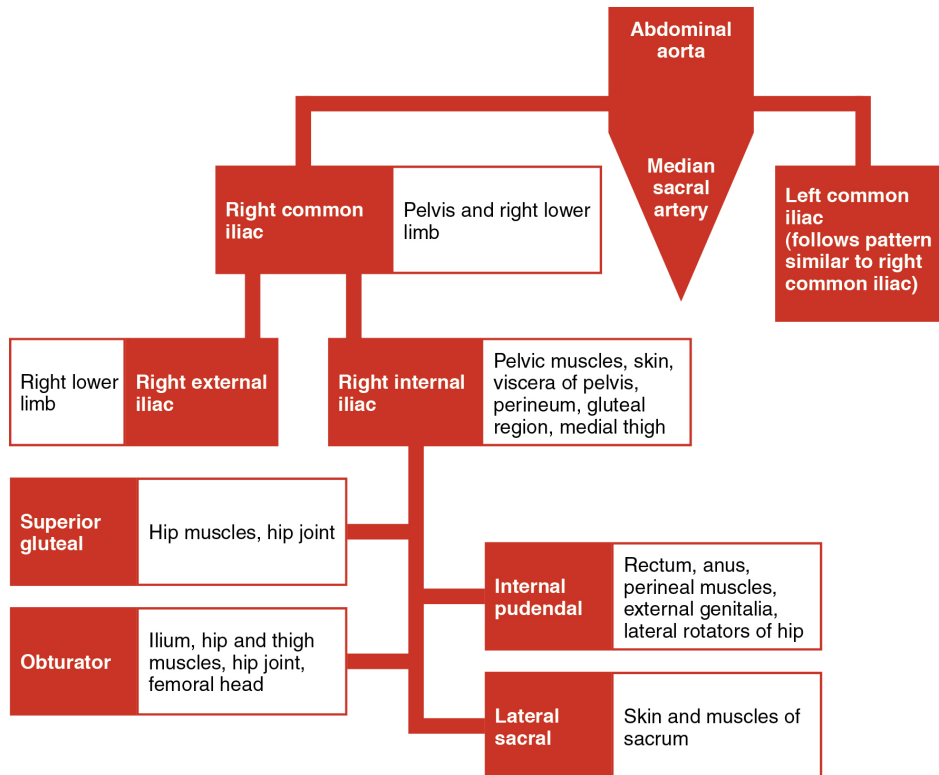
The aorta divides at approximately the level of vertebra L4 into a left and a right **common iliac artery** but continues as a small vessel, the **median sacral artery**, into the sacrum. The common iliac arteries provide blood to the pelvic region and ultimately to the lower limbs. They split into external and internal iliac arteries approximately at the level of the lumbar-sacral articulation. Each **internal iliac artery** sends branches to the urinary bladder, the walls of the pelvis, the external genitalia, and the medial portion of the femoral region. In females, they also provide blood to the uterus and vagina. The much larger **external iliac artery** supplies blood to each of the lower limbs. [\[link\]](#) shows the distribution of the major branches of the aorta into the thoracic and abdominal regions. [\[link\]](#) shows the distribution of the major branches of the common iliac arteries. [\[link\]](#) summarizes the major branches of the abdominal aorta.

Major Branches of the Aorta



The flow chart summarizes the distribution of the major branches of the aorta into the thoracic and abdominal regions.

Major Branches of the Iliac Arteries



The flow chart summarizes the distribution of the major branches of the common iliac arteries into the pelvis and lower limbs. The left side follows a similar pattern to the right.

| Vessels of the Abdominal Aorta | |
|--------------------------------|-------------|
| Vessel | Description |

| Vessels of the Abdominal Aorta | |
|---------------------------------------|---|
| Vessel | Description |
| Celiac trunk | Also called the celiac artery; a major branch of the abdominal aorta; gives rise to the left gastric artery, the splenic artery, and the common hepatic artery that forms the hepatic artery to the liver, the right gastric artery to the stomach, and the cystic artery to the gall bladder |
| Left gastric artery | Branch of the celiac trunk; supplies blood to the stomach |
| Splenic artery | Branch of the celiac trunk; supplies blood to the spleen |
| Common hepatic artery | Branch of the celiac trunk that forms the hepatic artery, the right gastric artery, and the cystic artery |
| Hepatic artery proper | Branch of the common hepatic artery; supplies systemic blood to the liver |
| Right gastric artery | Branch of the common hepatic artery; supplies blood to the stomach |
| Cystic artery | Branch of the common hepatic artery; supplies blood to the gall bladder |
| Superior mesenteric artery | Branch of the abdominal aorta; supplies blood to the small intestine (duodenum, jejunum, and ileum), the pancreas, and a majority of the large intestine |

| Vessels of the Abdominal Aorta | |
|---------------------------------------|---|
| Vessel | Description |
| Inferior mesenteric artery | Branch of the abdominal aorta; supplies blood to the distal segment of the large intestine and rectum |
| Inferior phrenic arteries | Branches of the abdominal aorta; supply blood to the inferior surface of the diaphragm |
| Adrenal artery | Branch of the abdominal aorta; supplies blood to the adrenal (suprarenal) glands |
| Renal artery | Branch of the abdominal aorta; supplies each kidney |
| Gonadal artery | Branch of the abdominal aorta; supplies blood to the gonads or reproductive organs; also described as ovarian arteries or testicular arteries, depending upon the sex of the individual |
| Ovarian artery | Branch of the abdominal aorta; supplies blood to ovary, uterine (Fallopian) tube, and uterus |
| Testicular artery | Branch of the abdominal aorta; ultimately travels outside the body cavity to the testes and forms one component of the spermatic cord |
| Lumbar arteries | Branches of the abdominal aorta; supply blood to the lumbar region, the abdominal wall, and spinal cord |
| Common iliac artery | Branch of the aorta that leads to the internal and external iliac arteries |

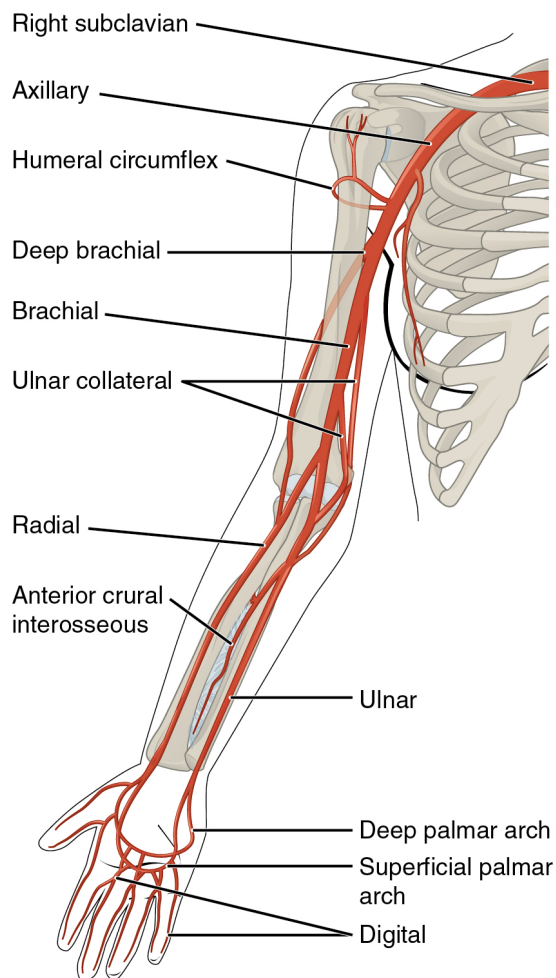
| Vessels of the Abdominal Aorta | |
|--------------------------------|---|
| Vessel | Description |
| Median sacral artery | Continuation of the aorta into the sacrum |
| Internal iliac artery | Branch from the common iliac arteries; supplies blood to the urinary bladder, walls of the pelvis, external genitalia, and the medial portion of the femoral region; in females, also provides blood to the uterus and vagina |
| External iliac artery | Branch of the common iliac artery that leaves the body cavity and becomes a femoral artery; supplies blood to the lower limbs |

Arteries Serving the Upper Limbs

As the subclavian artery exits the thorax into the axillary region, it is renamed the **axillary artery**. Although it does branch and supply blood to the region near the head of the humerus (via the humeral circumflex arteries), the majority of the vessel continues into the upper arm, or brachium, and becomes the brachial artery ([\[link\]](#)). The **brachial artery** supplies blood to much of the brachial region and divides at the elbow into several smaller branches, including the deep brachial arteries, which provide blood to the posterior surface of the arm, and the ulnar collateral arteries, which supply blood to the region of the elbow. As the brachial artery approaches the coronoid fossa, it bifurcates into the radial and ulnar arteries, which continue into the forearm, or antebrachium. The **radial artery** and **ulnar artery** parallel their namesake bones, giving off smaller branches until they reach the wrist, or carpal region. At this level, they fuse to form the superficial and deep **palmar arches** that supply blood to the hand, as well as the **digital arteries** that supply blood to the digits. [\[link\]](#)

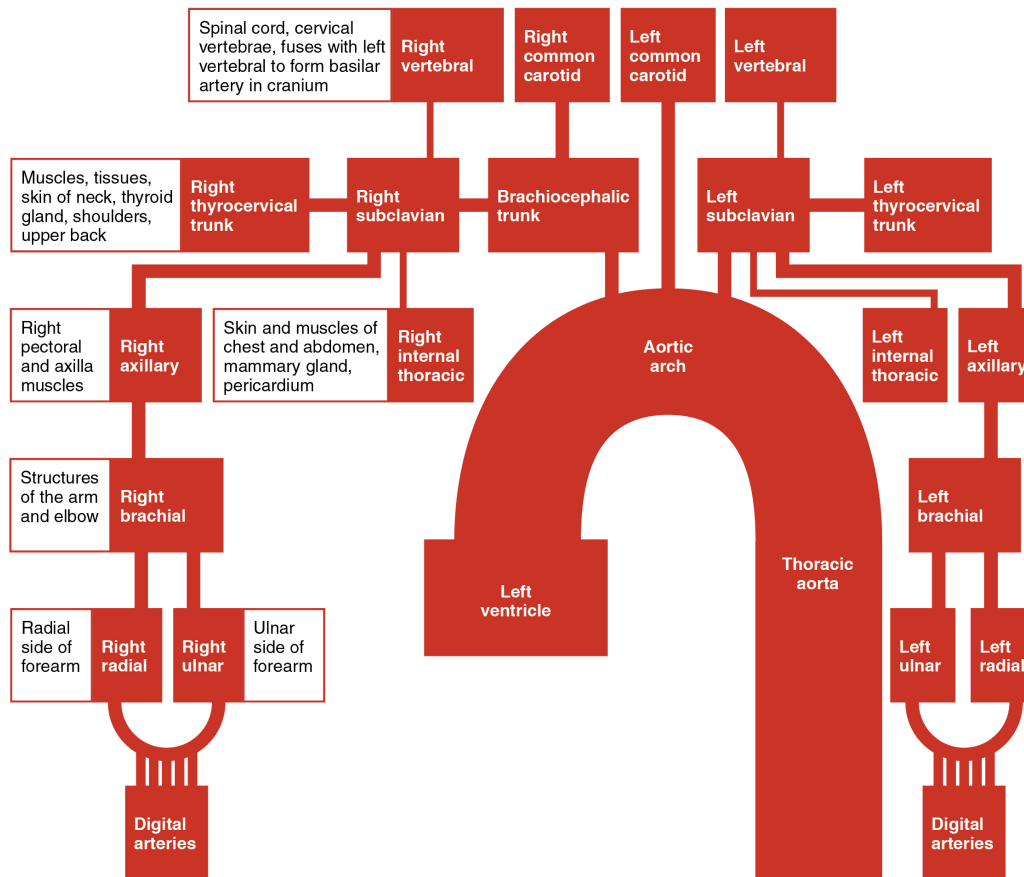
shows the distribution of systemic arteries from the heart into the upper limb. [\[link\]](#) summarizes the arteries serving the upper limbs.

Major Arteries Serving the Thorax and Upper Limb



The arteries that supply blood to the arms and hands are extensions of the subclavian arteries.

Major Arteries of the Upper Limb



The flow chart summarizes the distribution of the major arteries from the heart into the upper limb.

Arteries Serving the Upper Limbs

| Vessel | Description |
|--------|-------------|
|--------|-------------|

Arteries Serving the Upper Limbs

| Vessel | Description |
|--------------------------------------|---|
| Axillary artery | Continuation of the subclavian artery as it penetrates the body wall and enters the axillary region; supplies blood to the region near the head of the humerus (humeral circumflex arteries); the majority of the vessel continues into the brachium and becomes the brachial artery |
| Brachial artery | Continuation of the axillary artery in the brachium; supplies blood to much of the brachial region; gives off several smaller branches that provide blood to the posterior surface of the arm in the region of the elbow; bifurcates into the radial and ulnar arteries at the coronoid fossa |
| Radial artery | Formed at the bifurcation of the brachial artery; parallels the radius; gives off smaller branches until it reaches the carpal region where it fuses with the ulnar artery to form the superficial and deep palmar arches; supplies blood to the lower arm and carpal region |
| Ulnar artery | Formed at the bifurcation of the brachial artery; parallels the ulna; gives off smaller branches until it reaches the carpal region where it fuses with the radial artery to form the superficial and deep palmar arches; supplies blood to the lower arm and carpal region |
| Palmar arches (superficial and deep) | Formed from anastomosis of the radial and ulnar arteries; supply blood to the hand and digital arteries |

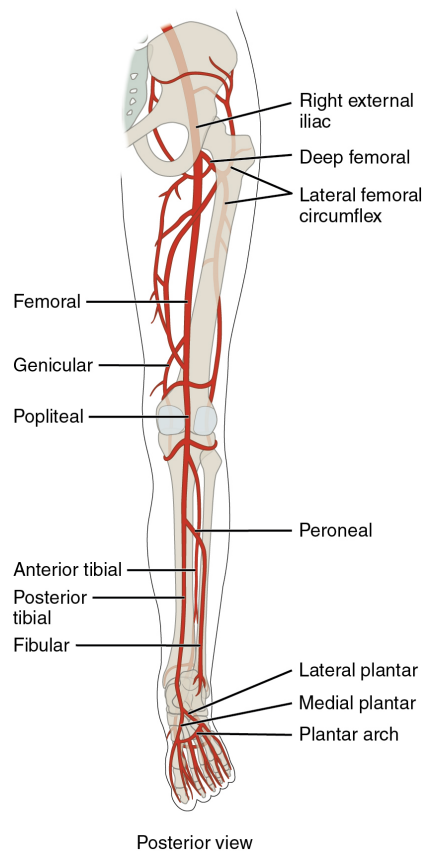
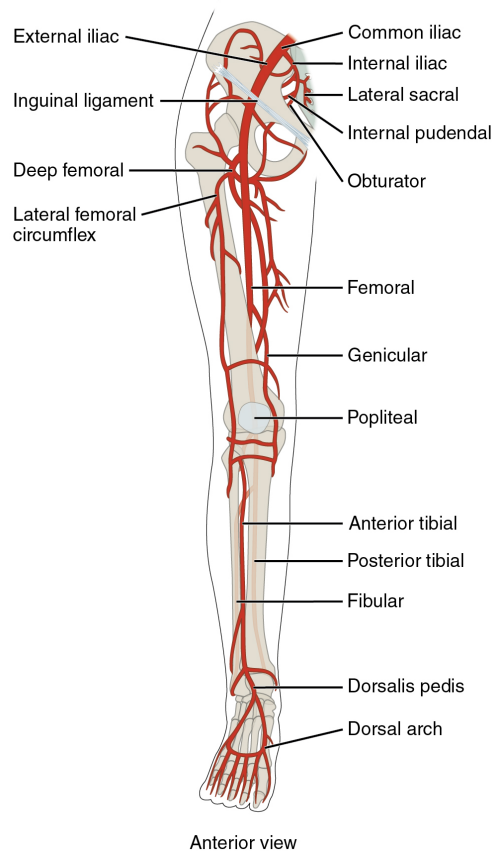
| Arteries Serving the Upper Limbs | |
|----------------------------------|--|
| Vessel | Description |
| Digital arteries | Formed from the superficial and deep palmar arches; supply blood to the digits |

Arteries Serving the Lower Limbs

The external iliac artery exits the body cavity and enters the femoral region of the lower leg ([\[link\]](#)). As it passes through the body wall, it is renamed the **femoral artery**. It gives off several smaller branches as well as the lateral **deep femoral artery** that in turn gives rise to a **lateral circumflex artery**. These arteries supply blood to the deep muscles of the thigh as well as ventral and lateral regions of the integument. The femoral artery also gives rise to the **genicular artery**, which provides blood to the region of the knee. As the femoral artery passes posterior to the knee near the popliteal fossa, it is called the popliteal artery. The **popliteal artery** branches into the anterior and posterior tibial arteries.

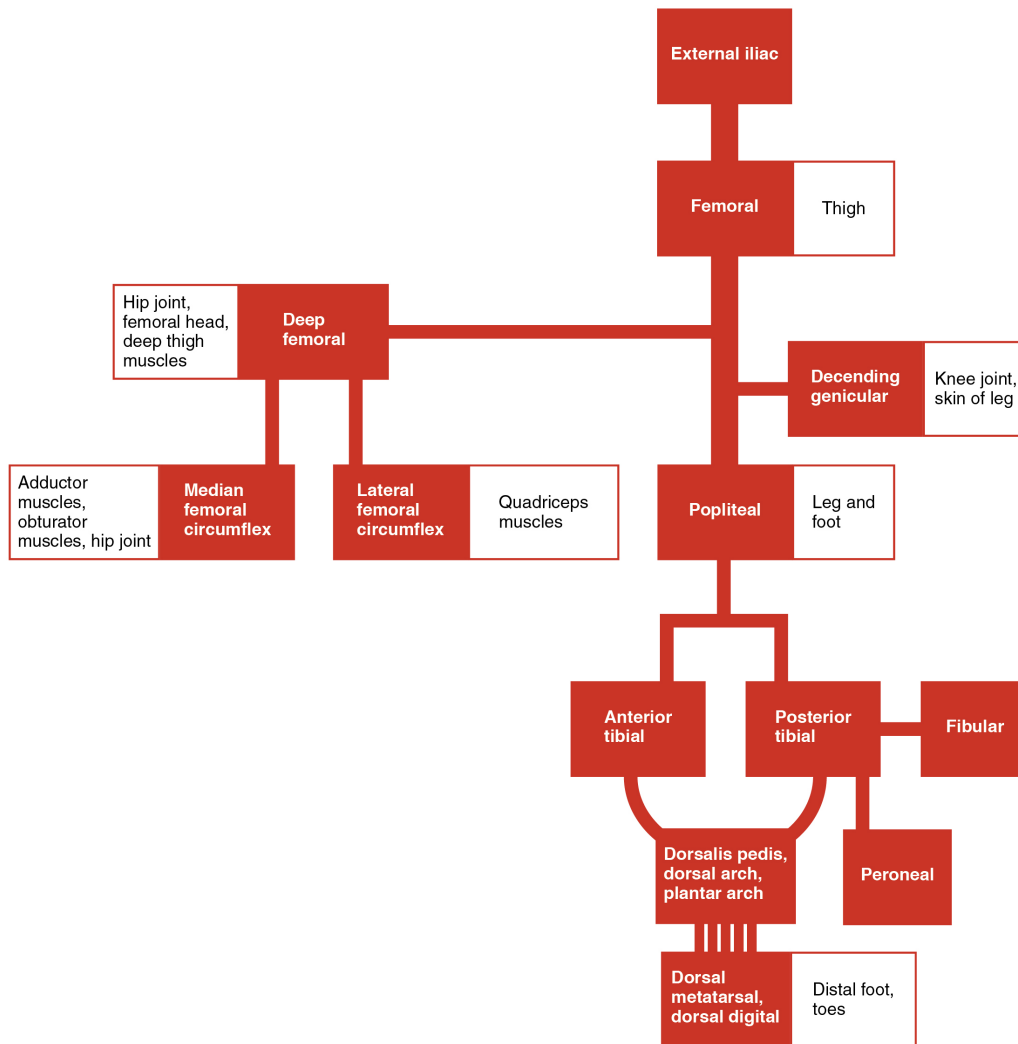
The **anterior tibial artery** is located between the tibia and fibula, and supplies blood to the muscles and integument of the anterior tibial region. Upon reaching the tarsal region, it becomes the **dorsalis pedis artery**, which branches repeatedly and provides blood to the tarsal and dorsal regions of the foot. The **posterior tibial artery** provides blood to the muscles and integument on the posterior surface of the tibial region. The fibular or peroneal artery branches from the posterior tibial artery. It bifurcates and becomes the **medial plantar artery** and **lateral plantar artery**, providing blood to the plantar surfaces. There is an anastomosis with the dorsalis pedis artery, and the medial and lateral plantar arteries form two arches called the **dorsal arch** (also called the arcuate arch) and the **plantar arch**, which provide blood to the remainder of the foot and toes. [\[link\]](#) shows the distribution of the major systemic arteries in the lower limb. [\[link\]](#) summarizes the major systemic arteries discussed in the text.

Major Arteries Serving the Lower Limb



Major arteries serving the lower limb are shown in anterior and posterior views.

Systemic Arteries of the Lower Limb



The flow chart summarizes the distribution of the systemic arteries from the external iliac artery into the lower limb.

| Arteries Serving the Lower Limbs | |
|----------------------------------|-------------|
| Vessel | Description |

Arteries Serving the Lower Limbs

| Vessel | Description |
|---------------------------|--|
| Femoral artery | Continuation of the external iliac artery after it passes through the body cavity; divides into several smaller branches, the lateral deep femoral artery, and the genicular artery; becomes the popliteal artery as it passes posterior to the knee |
| Deep femoral artery | Branch of the femoral artery; gives rise to the lateral circumflex arteries |
| Lateral circumflex artery | Branch of the deep femoral artery; supplies blood to the deep muscles of the thigh and the ventral and lateral regions of the integument |
| Genicular artery | Branch of the femoral artery; supplies blood to the region of the knee |
| Popliteal artery | Continuation of the femoral artery posterior to the knee; branches into the anterior and posterior tibial arteries |
| Anterior tibial artery | Branches from the popliteal artery; supplies blood to the anterior tibial region; becomes the dorsalis pedis artery |
| Dorsalis pedis artery | Forms from the anterior tibial artery; branches repeatedly to supply blood to the tarsal and dorsal regions of the foot |
| Posterior tibial artery | Branches from the popliteal artery and gives rise to the fibular or peroneal artery; supplies blood to the posterior tibial region |

| Arteries Serving the Lower Limbs | |
|---|--|
| Vessel | Description |
| Medial plantar artery | Arises from the bifurcation of the posterior tibial arteries; supplies blood to the medial plantar surfaces of the foot |
| Lateral plantar artery | Arises from the bifurcation of the posterior tibial arteries; supplies blood to the lateral plantar surfaces of the foot |
| Dorsal or arcuate arch | Formed from the anastomosis of the dorsalis pedis artery and the medial and plantar arteries; branches supply the distal portions of the foot and digits |
| Plantar arch | Formed from the anastomosis of the dorsalis pedis artery and the medial and plantar arteries; branches supply the distal portions of the foot and digits |

Overview of Systemic Veins

Systemic veins return blood to the right atrium. Since the blood has already passed through the systemic capillaries, it will be relatively low in oxygen concentration. In many cases, there will be veins draining organs and regions of the body with the same name as the arteries that supplied these regions and the two often parallel one another. This is often described as a “complementary” pattern. However, there is a great deal more variability in the venous circulation than normally occurs in the arteries. For the sake of brevity and clarity, this text will discuss only the most commonly encountered patterns. However, keep this variation in mind when you move from the classroom to clinical practice.

In both the neck and limb regions, there are often both superficial and deeper levels of veins. The deeper veins generally correspond to the complementary arteries. The superficial veins do not normally have direct

arterial counterparts, but in addition to returning blood, they also make contributions to the maintenance of body temperature. When the ambient temperature is warm, more blood is diverted to the superficial veins where heat can be more easily dissipated to the environment. In colder weather, there is more constriction of the superficial veins and blood is diverted deeper where the body can retain more of the heat.

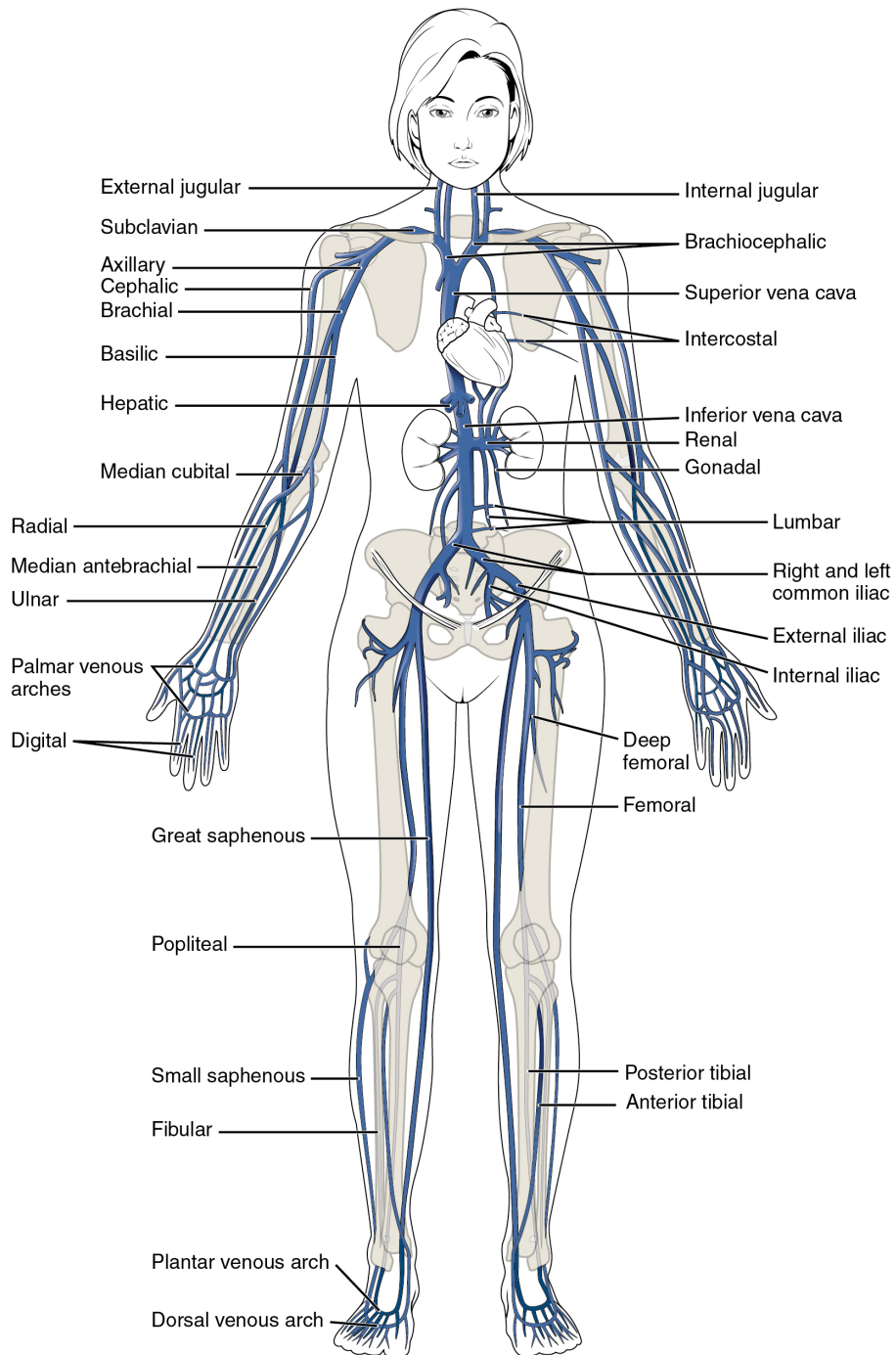
The “Voyage of Discovery” analogy and stick drawings mentioned earlier remain valid techniques for the study of systemic veins, but veins present a more difficult challenge because there are numerous anastomoses and multiple branches. It is like following a river with many tributaries and channels, several of which interconnect. Tracing blood flow through arteries follows the current in the direction of blood flow, so that we move from the heart through the large arteries and into the smaller arteries to the capillaries. From the capillaries, we move into the smallest veins and follow the direction of blood flow into larger veins and back to the heart. [\[link\]](#) outlines the path of the major systemic veins.

Note:



Visit this [site](#) for a brief online summary of the veins.

Major Systemic Veins of the Body



The major systemic veins of the body are shown here in an anterior view.

The right atrium receives all of the systemic venous return. Most of the blood flows into either the superior vena cava or inferior vena cava. If you draw an imaginary line at the level of the diaphragm, systemic venous circulation from above that line will generally flow into the superior vena cava; this includes blood from the head, neck, chest, shoulders, and upper limbs. The exception to this is that most venous blood flow from the coronary veins flows directly into the coronary sinus and from there directly into the right atrium. Beneath the diaphragm, systemic venous flow enters the inferior vena cava, that is, blood from the abdominal and pelvic regions and the lower limbs.

The Superior Vena Cava

The **superior vena cava** drains most of the body superior to the diaphragm ([\[link\]](#)). On both the left and right sides, the **subclavian vein** forms when the axillary vein passes through the body wall from the axillary region. It fuses with the external and internal jugular veins from the head and neck to form the **brachiocephalic vein**. Each **vertebral vein** also flows into the brachiocephalic vein close to this fusion. These veins arise from the base of the brain and the cervical region of the spinal cord, and flow largely through the intervertebral foramina in the cervical vertebrae. They are the counterparts of the vertebral arteries. Each **internal thoracic vein**, also known as an internal mammary vein, drains the anterior surface of the chest wall and flows into the brachiocephalic vein.

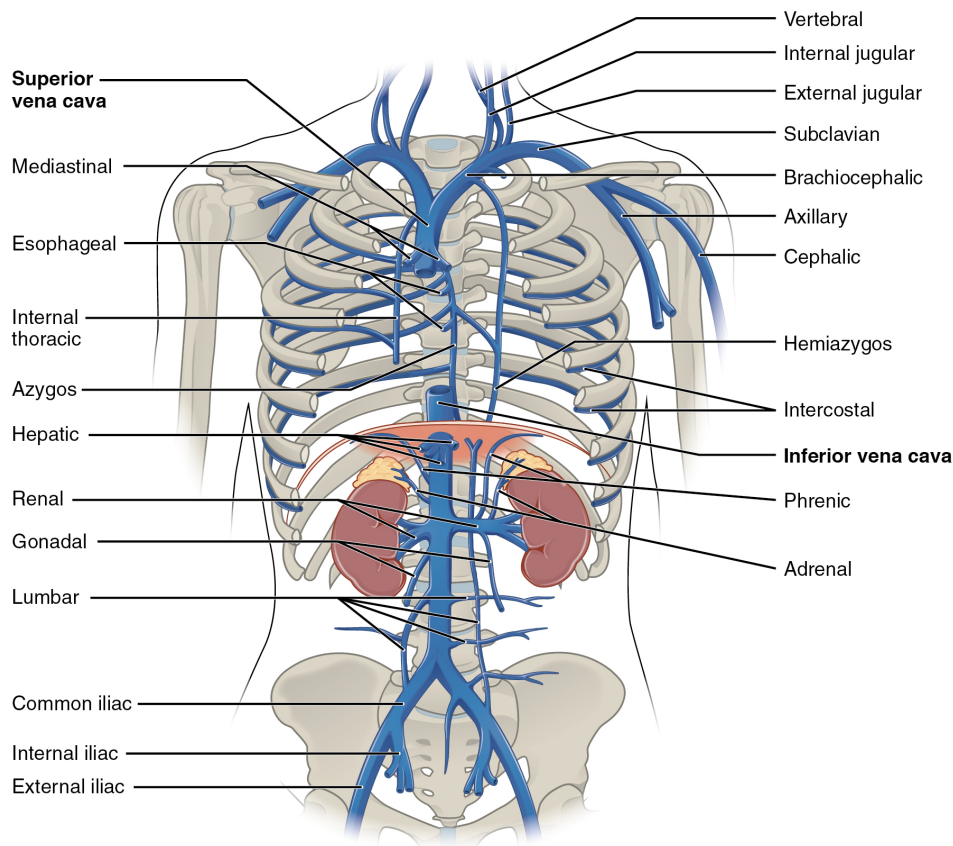
The remainder of the blood supply from the thorax drains into the azygos vein. Each **intercostal vein** drains muscles of the thoracic wall, each **esophageal vein** delivers blood from the inferior portions of the esophagus, each **bronchial vein** drains the systemic circulation from the lungs, and several smaller veins drain the mediastinal region. Bronchial veins carry approximately 13 percent of the blood that flows into the bronchial arteries; the remainder intermingles with the pulmonary circulation and returns to the heart via the pulmonary veins. These veins flow into the **azygos vein**, and with the smaller **hemiazygos vein** (hemi- = “half”) on the left of the vertebral column, drain blood from the thoracic region. The hemiazygos

vein does not drain directly into the superior vena cava but enters the brachiocephalic vein via the superior intercostal vein.

The azygos vein passes through the diaphragm from the thoracic cavity on the right side of the vertebral column and begins in the lumbar region of the thoracic cavity. It flows into the superior vena cava at approximately the level of T2, making a significant contribution to the flow of blood. It combines with the two large left and right brachiocephalic veins to form the superior vena cava.

[\[link\]](#) summarizes the veins of the thoracic region that flow into the superior vena cava.

Veins of the Thoracic and Abdominal Regions



Veins of the thoracic and abdominal regions drain blood from the area above the diaphragm, returning it to the right atrium via the superior vena cava.

| Veins of the Thoracic Region | |
|-------------------------------------|---|
| Vessel | Description |
| Superior vena cava | Large systemic vein; drains blood from most areas superior to the diaphragm; empties into the right atrium |
| Subclavian vein | Located deep in the thoracic cavity; formed by the axillary vein as it enters the thoracic cavity from the axillary region; drains the axillary and smaller local veins near the scapular region and leads to the brachiocephalic vein |
| Brachiocephalic veins | Pair of veins that form from a fusion of the external and internal jugular veins and the subclavian vein; subclavian, external and internal jugulars, vertebral, and internal thoracic veins flow into it; drain the upper thoracic region and lead to the superior vena cava |
| Vertebral vein | Arises from the base of the brain and the cervical region of the spinal cord; passes through the intervertebral foramina in the cervical vertebrae; drains smaller veins from the cranium, spinal cord, and vertebrae, and leads to the brachiocephalic vein; counterpart of the vertebral artery |

| Veins of the Thoracic Region | |
|-------------------------------------|---|
| Vessel | Description |
| Internal thoracic veins | Also called internal mammary veins; drain the anterior surface of the chest wall and lead to the brachiocephalic vein |
| Intercostal vein | Drains the muscles of the thoracic wall and leads to the azygos vein |
| Esophageal vein | Drains the inferior portions of the esophagus and leads to the azygos vein |
| Bronchial vein | Drains the systemic circulation from the lungs and leads to the azygos vein |
| Azygos vein | Originates in the lumbar region and passes through the diaphragm into the thoracic cavity on the right side of the vertebral column; drains blood from the intercostal veins, esophageal veins, bronchial veins, and other veins draining the mediastinal region, and leads to the superior vena cava |
| Hemiazygos vein | Smaller vein complementary to the azygos vein; drains the esophageal veins from the esophagus and the left intercostal veins, and leads to the brachiocephalic vein via the superior intercostal vein |

Veins of the Head and Neck

Blood from the brain and the superficial facial vein flow into each **internal jugular vein** ([\[link\]](#)). Blood from the more superficial portions of the head,

scalp, and cranial regions, including the **temporal vein** and **maxillary vein**, flow into each **external jugular vein**. Although the external and internal jugular veins are separate vessels, there are anastomoses between them close to the thoracic region. Blood from the external jugular vein empties into the subclavian vein. [\[link\]](#) summarizes the major veins of the head and neck.

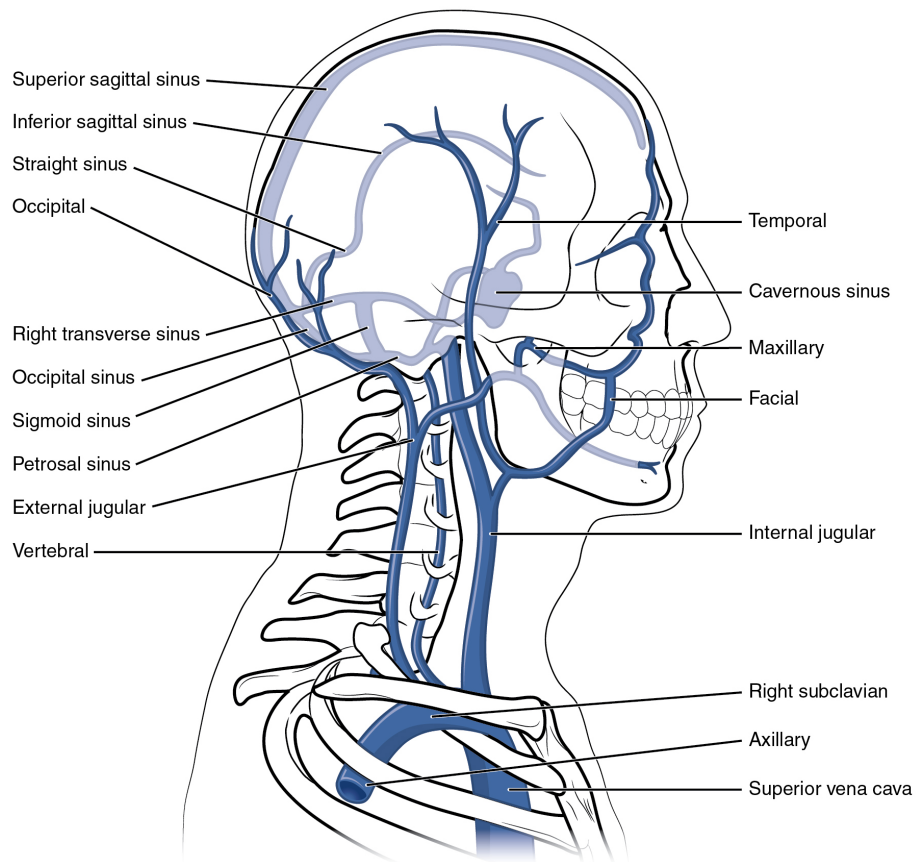
| Major Veins of the Head and Neck | |
|----------------------------------|---|
| Vessel | Description |
| Internal jugular vein | Parallel to the common carotid artery, which is more or less its counterpart, and passes through the jugular foramen and canal; primarily drains blood from the brain, receives the superficial facial vein, and empties into the subclavian vein |
| Temporal vein | Drains blood from the temporal region and flows into the external jugular vein |
| Maxillary vein | Drains blood from the maxillary region and flows into the external jugular vein |
| External jugular vein | Drains blood from the more superficial portions of the head, scalp, and cranial regions, and leads to the subclavian vein |

Venous Drainage of the Brain

Circulation to the brain is both critical and complex (see [\[link\]](#)). Many smaller veins of the brain stem and the superficial veins of the cerebrum lead to larger vessels referred to as intracranial sinuses. These include the superior and inferior sagittal sinuses, straight sinus, cavernous sinuses, left and right sinuses, the petrosal sinuses, and the occipital sinuses. Ultimately, sinuses will lead back to either the inferior jugular vein or vertebral vein.

Most of the veins on the superior surface of the cerebrum flow into the largest of the sinuses, the **superior sagittal sinus**. It is located midsagittally between the meningeal and periosteal layers of the dura mater within the falx cerebri and, at first glance in images or models, can be mistaken for the subarachnoid space. Most reabsorption of cerebrospinal fluid occurs via the chorionic villi (arachnoid granulations) into the superior sagittal sinus. Blood from most of the smaller vessels originating from the inferior cerebral veins flows into the **great cerebral vein** and into the **straight sinus**. Other cerebral veins and those from the eye socket flow into the **cavernous sinus**, which flows into the **petrosal sinus** and then into the internal jugular vein. The **occipital sinus**, sagittal sinus, and straight sinuses all flow into the left and right transverse sinuses near the lambdoid suture. The **transverse sinuses** in turn flow into the **sigmoid sinuses** that pass through the jugular foramen and into the internal jugular vein. The internal jugular vein flows parallel to the common carotid artery and is more or less its counterpart. It empties into the brachiocephalic vein. The veins draining the cervical vertebrae and the posterior surface of the skull, including some blood from the occipital sinus, flow into the vertebral veins. These parallel the vertebral arteries and travel through the transverse foramina of the cervical vertebrae. The vertebral veins also flow into the brachiocephalic veins. [\[link\]](#) summarizes the major veins of the brain.

Veins of the Head and Neck



This left lateral view shows the veins of the head and neck, including the intercranial sinuses.

Major Veins of the Brain

| Vessel | Description |
|--------|-------------|
|--------|-------------|

| Major Veins of the Brain | |
|---------------------------------|---|
| Vessel | Description |
| Superior sagittal sinus | Enlarged vein located midsagittally between the meningeal and periosteal layers of the dura mater within the falx cerebri; receives most of the blood drained from the superior surface of the cerebrum and leads to the inferior jugular vein and the vertebral vein |
| Great cerebral vein | Receives most of the smaller vessels from the inferior cerebral veins and leads to the straight sinus |
| Straight sinus | Enlarged vein that drains blood from the brain; receives most of the blood from the great cerebral vein and leads to the left or right transverse sinus |
| Cavernous sinus | Enlarged vein that receives blood from most of the other cerebral veins and the eye socket, and leads to the petrosal sinus |
| Petrosal sinus | Enlarged vein that receives blood from the cavernous sinus and leads into the internal jugular veins |
| Occipital sinus | Enlarged vein that drains the occipital region near the falx cerebelli and leads to the left and right transverse sinuses, and also the vertebral veins |
| Transverse sinuses | Pair of enlarged veins near the lambdoid suture that drains the occipital, sagittal, and straight sinuses, and leads to the sigmoid sinuses |

| Major Veins of the Brain | |
|--------------------------|--|
| Vessel | Description |
| Sigmoid sinuses | Enlarged vein that receives blood from the transverse sinuses and leads through the jugular foramen to the internal jugular vein |

Veins Draining the Upper Limbs

The **digital veins** in the fingers come together in the hand to form the **palmar venous arches** ([\[link\]](#)). From here, the veins come together to form the radial vein, the ulnar vein, and the median antebrachial vein. The **radial vein** and the **ulnar vein** parallel the bones of the forearm and join together at the antebrachium to form the **brachial vein**, a deep vein that flows into the axillary vein in the brachium.

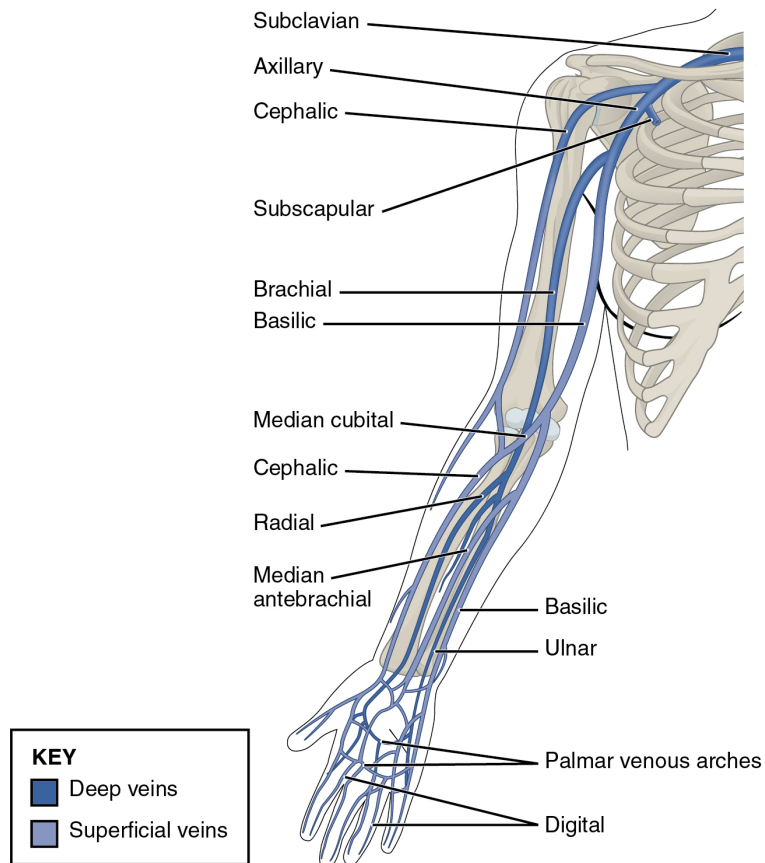
The **median antebrachial vein** parallels the ulnar vein, is more medial in location, and joins the **basilic vein** in the forearm. As the basilic vein reaches the antecubital region, it gives off a branch called the **median cubital vein** that crosses at an angle to join the cephalic vein. The median cubital vein is the most common site for drawing venous blood in humans. The basilic vein continues through the arm medially and superficially to the axillary vein.

The **cephalic vein** begins in the antebrachium and drains blood from the superficial surface of the arm into the axillary vein. It is extremely superficial and easily seen along the surface of the biceps brachii muscle in individuals with good muscle tone and in those without excessive subcutaneous adipose tissue in the arms.

The **subscapular vein** drains blood from the subscapular region and joins the cephalic vein to form the **axillary vein**. As it passes through the body wall and enters the thorax, the axillary vein becomes the subclavian vein.

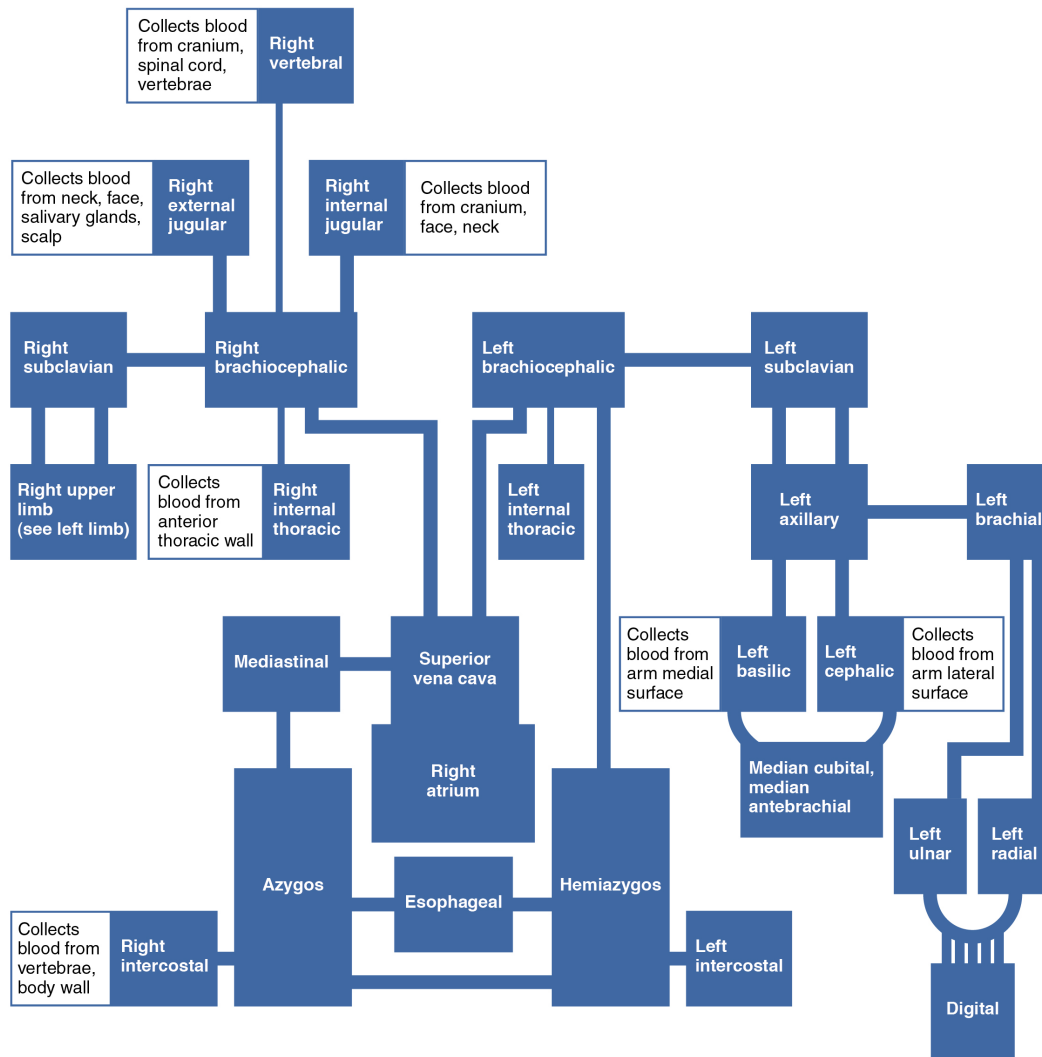
Many of the larger veins of the thoracic and abdominal region and upper limb are further represented in the flow chart in [\[link\]](#). [\[link\]](#) summarizes the veins of the upper limbs.

Veins of the Upper Limb



This anterior view shows the veins that drain the upper limb.

Veins Flowing into the Superior Vena Cava



The flow chart summarizes the distribution of the veins flowing into the superior vena cava.

Veins of the Upper Limbs

| Vessel of the Upper Limb | Description |
|---------------------------------|--------------------|
|---------------------------------|--------------------|

| Vessel | Description |
|--------------------------|---|
| Digital veins | Drain the digits and lead to the palmar arches of the hand and dorsal venous arch of the foot |
| Palmar venous arches | Drain the hand and digits, and lead to the radial vein, ulnar veins, and the median antebrachial vein |
| Radial vein | Vein that parallels the radius and radial artery; arises from the palmar venous arches and leads to the brachial vein |
| Ulnar vein | Vein that parallels the ulna and ulnar artery; arises from the palmar venous arches and leads to the brachial vein |
| Brachial vein | Deeper vein of the arm that forms from the radial and ulnar veins in the lower arm; leads to the axillary vein |
| Median antebrachial vein | Vein that parallels the ulnar vein but is more medial in location; intertwines with the palmar venous arches; leads to the basilic vein |
| Basilic vein | Superficial vein of the arm that arises from the median antebrachial vein, intersects with the median cubital vein, parallels the ulnar vein, and continues into the upper arm; along with the brachial vein, it leads to the axillary vein |

Veins of the Upper Limbs

| Vessel | Description |
|---------------------|--|
| Median cubital vein | Superficial vessel located in the antecubital region that links the cephalic vein to the basilic vein in the form of a v; a frequent site from which to draw blood |
| Cephalic vein | Superficial vessel in the upper arm; leads to the axillary vein |
| Subscapular vein | Drains blood from the subscapular region and leads to the axillary vein |
| Axillary vein | The major vein in the axillary region; drains the upper limb and becomes the subclavian vein |

The Inferior Vena Cava

Other than the small amount of blood drained by the azygos and hemiazygos veins, most of the blood inferior to the diaphragm drains into the inferior vena cava before it is returned to the heart (see [\[link\]](#)). Lying just beneath the parietal peritoneum in the abdominal cavity, the **inferior vena cava** parallels the abdominal aorta, where it can receive blood from abdominal veins. The lumbar portions of the abdominal wall and spinal cord are drained by a series of **lumbar veins**, usually four on each side. The ascending lumbar veins drain into either the azygos vein on the right or the hemiazygos vein on the left, and return to the superior vena cava. The remaining lumbar veins drain directly into the inferior vena cava.

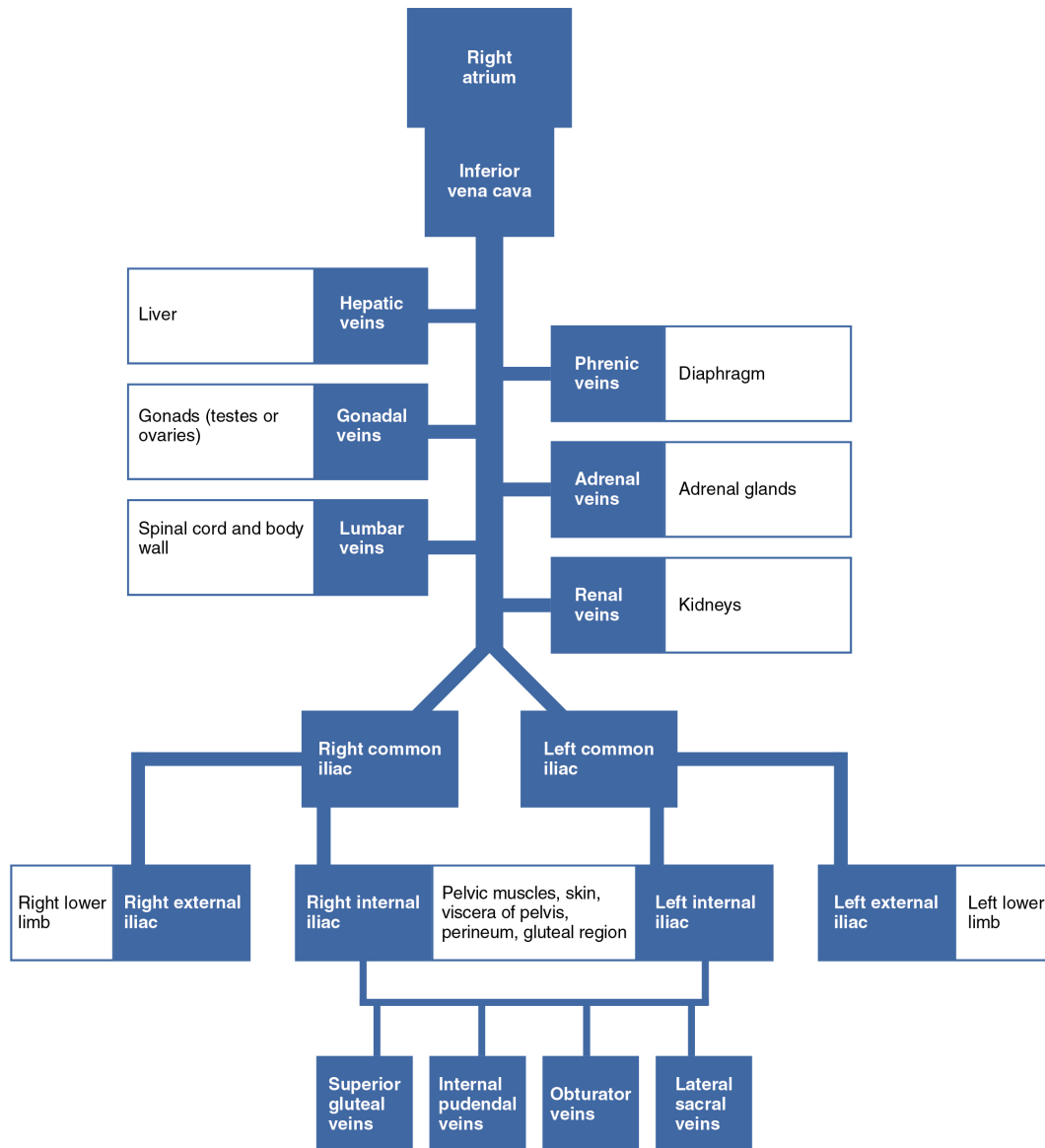
Blood supply from the kidneys flows into each **renal vein**, normally the largest veins entering the inferior vena cava. A number of other, smaller

veins empty into the left renal vein. Each **adrenal vein** drains the adrenal or suprarenal glands located immediately superior to the kidneys. The right adrenal vein enters the inferior vena cava directly, whereas the left adrenal vein enters the left renal vein.

From the male reproductive organs, each **testicular vein** flows from the scrotum, forming a portion of the spermatic cord. Each **ovarian vein** drains an ovary in females. Each of these veins is generically called a **gonadal vein**. The right gonadal vein empties directly into the inferior vena cava, and the left gonadal vein empties into the left renal vein.

Each side of the diaphragm drains into a **phrenic vein**; the right phrenic vein empties directly into the inferior vena cava, whereas the left phrenic vein empties into the left renal vein. Blood supply from the liver drains into each **hepatic vein** and directly into the inferior vena cava. Since the inferior vena cava lies primarily to the right of the vertebral column and aorta, the left renal vein is longer, as are the left phrenic, adrenal, and gonadal veins. The longer length of the left renal vein makes the left kidney the primary target of surgeons removing this organ for donation. [\[link\]](#) provides a flow chart of the veins flowing into the inferior vena cava. [\[link\]](#) summarizes the major veins of the abdominal region.

Venous Flow into Inferior Vena Cava



The flow chart summarizes veins that deliver blood to the inferior vena cava.

| Major Veins of the Abdominal Region | |
|--|---|
| Vessel | Description |
| Inferior vena cava | Large systemic vein that drains blood from areas largely inferior to the diaphragm; empties into the right atrium |
| Lumbar veins | Series of veins that drain the lumbar portion of the abdominal wall and spinal cord; the ascending lumbar veins drain into the azygos vein on the right or the hemiazygos vein on the left; the remaining lumbar veins drain directly into the inferior vena cava |
| Renal vein | Largest vein entering the inferior vena cava; drains the kidneys and flows into the inferior vena cava |
| Adrenal vein | Drains the adrenal or suprarenal; the right adrenal vein enters the inferior vena cava directly and the left adrenal vein enters the left renal vein |
| Testicular vein | Drains the testes and forms part of the spermatic cord; the right testicular vein empties directly into the inferior vena cava and the left testicular vein empties into the left renal vein |
| Ovarian vein | Drains the ovary; the right ovarian vein empties directly into the inferior vena cava and the left ovarian vein empties into the left renal vein |
| Gonadal vein | Generic term for a vein draining a reproductive organ; may be either an ovarian vein or a testicular vein, depending on the sex of the individual |

| Major Veins of the Abdominal Region | |
|-------------------------------------|---|
| Vessel | Description |
| Phrenic vein | Drains the diaphragm; the right phrenic vein flows into the inferior vena cava and the left phrenic vein empties into the left renal vein |
| Hepatic vein | Drains systemic blood from the liver and flows into the inferior vena cava |

Veins Draining the Lower Limbs

The superior surface of the foot drains into the digital veins, and the inferior surface drains into the **plantar veins**, which flow into a complex series of anastomoses in the feet and ankles, including the **dorsal venous arch** and the **plantar venous arch** ([\[link\]](#)). From the dorsal venous arch, blood supply drains into the anterior and posterior tibial veins. The **anterior tibial vein** drains the area near the tibialis anterior muscle and combines with the posterior tibial vein and the fibular vein to form the popliteal vein. The **posterior tibial vein** drains the posterior surface of the tibia and joins the popliteal vein. The **fibular vein** drains the muscles and integument in proximity to the fibula and also joins the popliteal vein. The **small saphenous vein** located on the lateral surface of the leg drains blood from the superficial regions of the lower leg and foot, and flows into to the **popliteal vein**. As the popliteal vein passes behind the knee in the popliteal region, it becomes the femoral vein. It is palpable in patients without excessive adipose tissue.

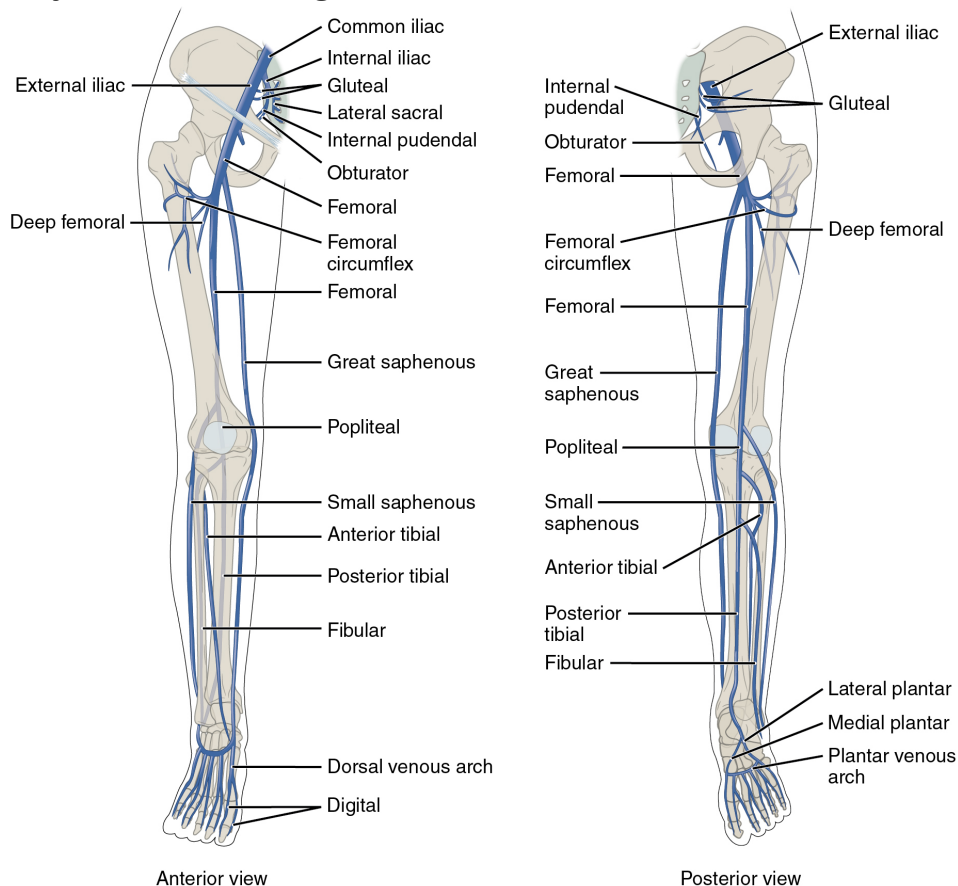
Close to the body wall, the great saphenous vein, the deep femoral vein, and the femoral circumflex vein drain into the femoral vein. The **great saphenous vein** is a prominent surface vessel located on the medial surface of the leg and thigh that collects blood from the superficial portions of these areas. The **deep femoral vein**, as the name suggests, drains blood from the deeper portions of the thigh. The **femoral circumflex vein** forms a loop

around the femur just inferior to the trochanters and drains blood from the areas in proximity to the head and neck of the femur.

As the **femoral vein** penetrates the body wall from the femoral portion of the upper limb, it becomes the **external iliac vein**, a large vein that drains blood from the leg to the common iliac vein. The pelvic organs and integument drain into the **internal iliac vein**, which forms from several smaller veins in the region, including the umbilical veins that run on either side of the bladder. The external and internal iliac veins combine near the inferior portion of the sacroiliac joint to form the common iliac vein. In addition to blood supply from the external and internal iliac veins, the **middle sacral vein** drains the sacral region into the **common iliac vein**. Similar to the common iliac arteries, the common iliac veins come together at the level of L5 to form the inferior vena cava.

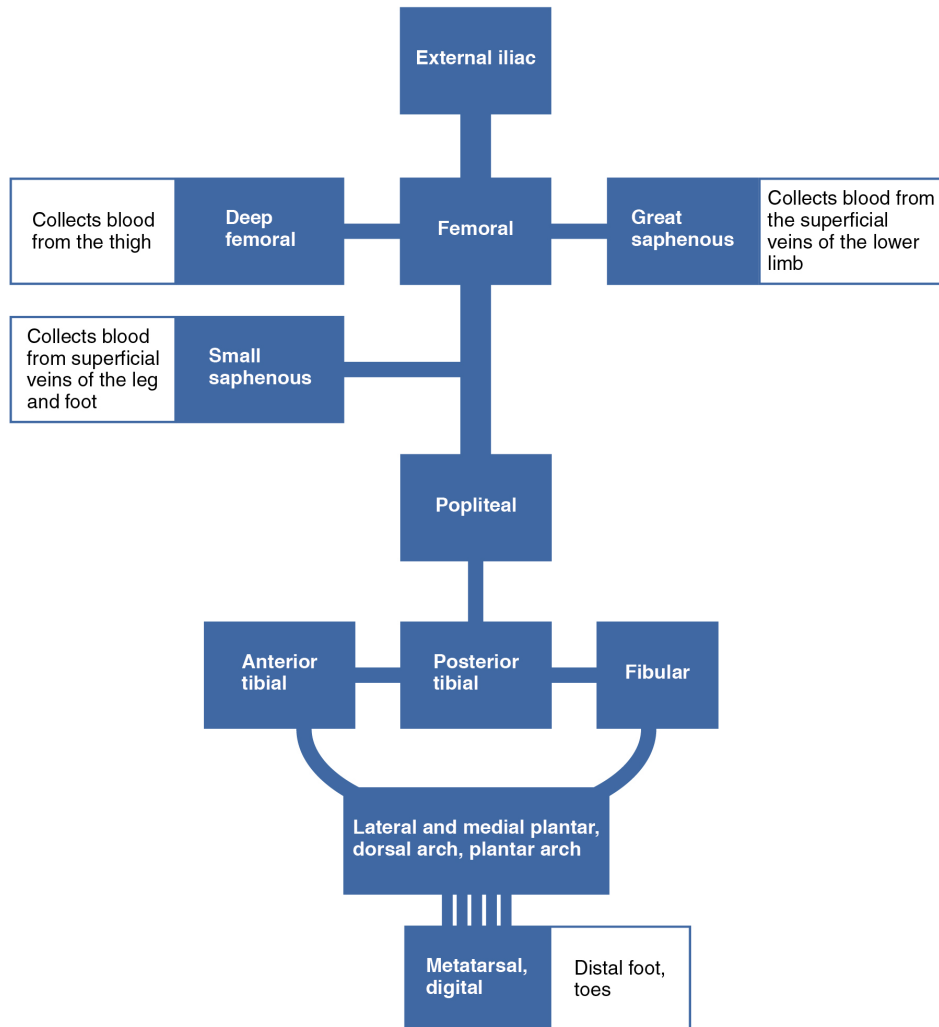
[\[link\]](#) is a flow chart of veins flowing into the lower limb. [\[link\]](#) summarizes the major veins of the lower limbs.

Major Veins Serving the Lower Limbs



Anterior and posterior views show the major veins that drain the lower limb into the inferior vena cava.

Major Veins of the Lower Limb



The flow chart summarizes venous flow from the lower limb.

| Veins of the Lower Limbs | |
|---------------------------------|---|
| Vessel | Description |
| Plantar veins | Drain the foot and flow into the plantar venous arch |
| Dorsal venous arch | Drains blood from digital veins and vessels on the superior surface of the foot |
| Plantar venous arch | Formed from the plantar veins; flows into the anterior and posterior tibial veins through anastomoses |
| Anterior tibial vein | Formed from the dorsal venous arch; drains the area near the tibialis anterior muscle and flows into the popliteal vein |
| Posterior tibial vein | Formed from the dorsal venous arch; drains the area near the posterior surface of the tibia and flows into the popliteal vein |
| Fibular vein | Drains the muscles and integument near the fibula and flows into the popliteal vein |
| Small saphenous vein | Located on the lateral surface of the leg; drains blood from the superficial regions of the lower leg and foot, and flows into the popliteal vein |
| Popliteal vein | Drains the region behind the knee and forms from the fusion of the fibular, anterior, and posterior tibial veins; flows into the femoral vein |

| Veins of the Lower Limbs | |
|---------------------------------|---|
| Vessel | Description |
| Great saphenous vein | Prominent surface vessel located on the medial surface of the leg and thigh; drains the superficial portions of these areas and flows into the femoral vein |
| Deep femoral vein | Drains blood from the deeper portions of the thigh and flows into the femoral vein |
| Femoral circumflex vein | Forms a loop around the femur just inferior to the trochanters; drains blood from the areas around the head and neck of the femur; flows into the femoral vein |
| Femoral vein | Drains the upper leg; receives blood from the great saphenous vein, the deep femoral vein, and the femoral circumflex vein; becomes the external iliac vein when it crosses the body wall |
| External iliac vein | Formed when the femoral vein passes into the body cavity; drains the legs and flows into the common iliac vein |
| Internal iliac vein | Drains the pelvic organs and integument; formed from several smaller veins in the region; flows into the common iliac vein |
| Middle sacral vein | Drains the sacral region and flows into the left common iliac vein |

| Veins of the Lower Limbs | |
|--------------------------|---|
| Vessel | Description |
| Common iliac vein | Flows into the inferior vena cava at the level of L5; the left common iliac vein drains the sacral region; formed from the union of the external and internal iliac veins near the inferior portion of the sacroiliac joint |

Hepatic Portal System

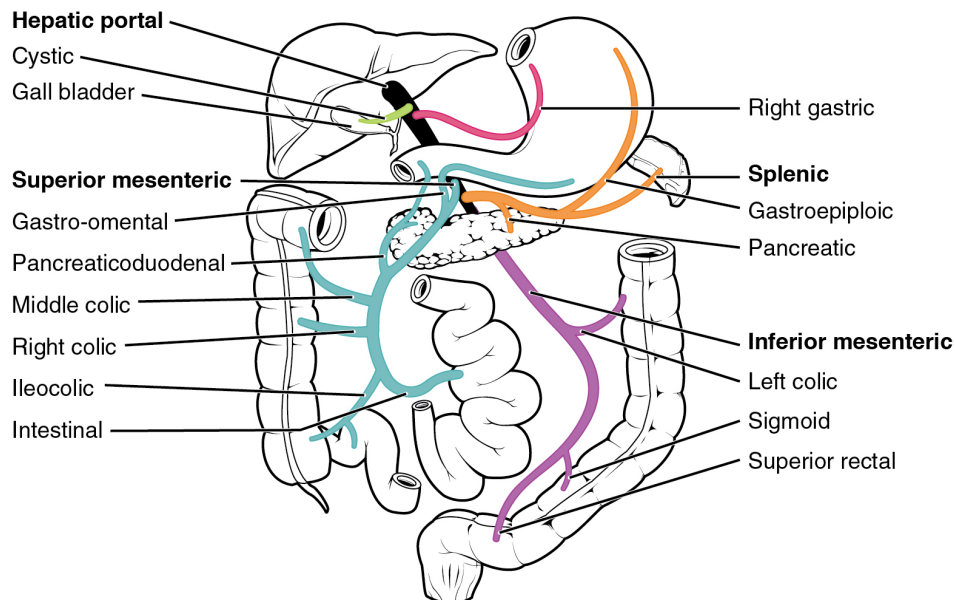
The liver is a complex biochemical processing plant. It packages nutrients absorbed by the digestive system; produces plasma proteins, clotting factors, and bile; and disposes of worn-out cell components and waste products. Instead of entering the circulation directly, absorbed nutrients and certain wastes (for example, materials produced by the spleen) travel to the liver for processing. They do so via the **hepatic portal system** ([link](#)). Portal systems begin and end in capillaries. In this case, the initial capillaries from the stomach, small intestine, large intestine, and spleen lead to the hepatic portal vein and end in specialized capillaries within the liver, the hepatic sinusoids. You saw the only other portal system with the hypothalamic-hypophyseal portal vessel in the endocrine chapter.

The hepatic portal system consists of the hepatic portal vein and the veins that drain into it. The hepatic portal vein itself is relatively short, beginning at the level of L2 with the confluence of the superior mesenteric and splenic veins. It also receives branches from the inferior mesenteric vein, plus the splenic veins and all their tributaries. The superior mesenteric vein receives blood from the small intestine, two-thirds of the large intestine, and the stomach. The inferior mesenteric vein drains the distal third of the large intestine, including the descending colon, the sigmoid colon, and the rectum. The splenic vein is formed from branches from the spleen, pancreas, and portions of the stomach, and the inferior mesenteric vein. After its formation, the hepatic portal vein also receives branches from the gastric veins of the stomach and cystic veins from the gall bladder. The

hepatic portal vein delivers materials from these digestive and circulatory organs directly to the liver for processing.

Because of the hepatic portal system, the liver receives its blood supply from two different sources: from normal systemic circulation via the hepatic artery and from the hepatic portal vein. The liver processes the blood from the portal system to remove certain wastes and excess nutrients, which are stored for later use. This processed blood, as well as the systemic blood that came from the hepatic artery, exits the liver via the right, left, and middle hepatic veins, and flows into the inferior vena cava. Overall systemic blood composition remains relatively stable, since the liver is able to metabolize the absorbed digestive components.

Hepatic Portal System



The liver receives blood from the normal systemic circulation via the hepatic artery. It also receives and processes blood from other organs, delivered via the veins of the hepatic portal system. All blood exits the liver via the hepatic vein, which delivers the blood to the inferior vena cava. (Different colors are used to help distinguish among the different vessels in the system.)

Chapter Review

The right ventricle pumps oxygen-depleted blood into the pulmonary trunk and right and left pulmonary arteries, which carry it to the right and left lungs for gas exchange. Oxygen-rich blood is transported by pulmonary veins to the left atrium. The left ventricle pumps this blood into the aorta. The main regions of the aorta are the ascending aorta, aortic arch, and descending aorta, which is further divided into the thoracic and abdominal aorta. The coronary arteries branch from the ascending aorta. After oxygenating tissues in the capillaries, systemic blood is returned to the right atrium from the venous system via the superior vena cava, which drains most of the veins superior to the diaphragm, the inferior vena cava, which drains most of the veins inferior to the diaphragm, and the coronary veins via the coronary sinus. The hepatic portal system carries blood to the liver for processing before it enters circulation. Review the figures provided in this section for circulation of blood through the blood vessels.

Review Questions

Exercise:

Problem: The coronary arteries branch off of the _____.

- a. aortic valve
- b. ascending aorta
- c. aortic arch
- d. thoracic aorta

Solution:

B

Exercise:

Problem: Which of the following statements is true?

- a. The left and right common carotid arteries both branch off of the brachiocephalic trunk.
- b. The brachial artery is the distal branch of the axillary artery.
- c. The radial and ulnar arteries join to form the palmar arch.
- d. All of the above are true.

Solution:

C

Exercise:

Problem:

Arteries serving the stomach, pancreas, and liver all branch from the _____.

- a. superior mesenteric artery
- b. inferior mesenteric artery
- c. celiac trunk
- d. splenic artery

Solution:

C

Exercise:

Problem: The right and left brachiocephalic veins _____.

- a. drain blood from the right and left internal jugular veins
- b. drain blood from the right and left subclavian veins
- c. drain into the superior vena cava
- d. all of the above are true

Solution:

D

Exercise:

Problem:

The hepatic portal system delivers blood from the digestive organs to the _____.

- a. liver
- b. hypothalamus
- c. spleen
- d. left atrium

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

Identify the ventricle of the heart that pumps oxygen-depleted blood and the arteries of the body that carry oxygen-depleted blood.

Solution:

The right ventricle of the heart pumps oxygen-depleted blood to the pulmonary arteries.

Exercise:

Problem:What organs do the gonadal veins drain?

Solution:

The gonadal veins drain the testes in males and the ovaries in females.

Exercise:

Problem:

What arteries play the leading roles in supplying blood to the brain?

Solution:

The internal carotid arteries and the vertebral arteries provide most of the brain's blood supply.

Glossary

abdominal aorta

portion of the aorta inferior to the aortic hiatus and superior to the common iliac arteries

adrenal artery

branch of the abdominal aorta; supplies blood to the adrenal (suprarenal) glands

adrenal vein

drains the adrenal or suprarenal glands that are immediately superior to the kidneys; the right adrenal vein enters the inferior vena cava directly and the left adrenal vein enters the left renal vein

anterior cerebral artery

arises from the internal carotid artery; supplies the frontal lobe of the cerebrum

anterior communicating artery

anastomosis of the right and left internal carotid arteries; supplies blood to the brain

anterior tibial artery

branches from the popliteal artery; supplies blood to the anterior tibial region; becomes the dorsalis pedis artery

anterior tibial vein

forms from the dorsal venous arch; drains the area near the tibialis anterior muscle and leads to the popliteal vein

aorta

largest artery in the body, originating from the left ventricle and descending to the abdominal region where it bifurcates into the common iliac arteries at the level of the fourth lumbar vertebra; arteries originating from the aorta distribute blood to virtually all tissues of the body

aortic arch

arc that connects the ascending aorta to the descending aorta; ends at the intervertebral disk between the fourth and fifth thoracic vertebrae

aortic hiatus

opening in the diaphragm that allows passage of the thoracic aorta into the abdominal region where it becomes the abdominal aorta

arterial circle

(also, circle of Willis) anastomosis located at the base of the brain that ensures continual blood supply; formed from branches of the internal carotid and vertebral arteries; supplies blood to the brain

ascending aorta

initial portion of the aorta, rising from the left ventricle for a distance of approximately 5 cm

axillary artery

continuation of the subclavian artery as it penetrates the body wall and enters the axillary region; supplies blood to the region near the head of the humerus (humeral circumflex arteries); the majority of the vessel continues into the brachium and becomes the brachial artery

axillary vein

major vein in the axillary region; drains the upper limb and becomes the subclavian vein

azygos vein

originates in the lumbar region and passes through the diaphragm into the thoracic cavity on the right side of the vertebral column; drains blood from the intercostal veins, esophageal veins, bronchial veins, and other veins draining the mediastinal region; leads to the superior vena cava

basilar artery

formed from the fusion of the two vertebral arteries; sends branches to the cerebellum, brain stem, and the posterior cerebral arteries; the main blood supply to the brain stem

basilic vein

superficial vein of the arm that arises from the palmar venous arches, intersects with the median cubital vein, parallels the ulnar vein, and continues into the upper arm; along with the brachial vein, it leads to the axillary vein

brachial artery

continuation of the axillary artery in the brachium; supplies blood to much of the brachial region; gives off several smaller branches that provide blood to the posterior surface of the arm in the region of the elbow; bifurcates into the radial and ulnar arteries at the coronoid fossa

brachial vein

deeper vein of the arm that forms from the radial and ulnar veins in the lower arm; leads to the axillary vein

brachiocephalic artery

single vessel located on the right side of the body; the first vessel branching from the aortic arch; gives rise to the right subclavian artery and the right common carotid artery; supplies blood to the head, neck, upper limb, and wall of the thoracic region

brachiocephalic vein

one of a pair of veins that form from a fusion of the external and internal jugular veins and the subclavian vein; subclavian, external and internal jugulars, vertebral, and internal thoracic veins lead to it; drains the upper thoracic region and flows into the superior vena cava

bronchial artery

systemic branch from the aorta that provides oxygenated blood to the lungs in addition to the pulmonary circuit

bronchial vein

drains the systemic circulation from the lungs and leads to the azygos vein

cavernous sinus

enlarged vein that receives blood from most of the other cerebral veins and the eye socket, and leads to the petrosal sinus

celiac trunk

(also, celiac artery) major branch of the abdominal aorta; gives rise to the left gastric artery, the splenic artery, and the common hepatic artery that forms the hepatic artery to the liver, the right gastric artery to the stomach, and the cystic artery to the gall bladder

cephalic vein

superficial vessel in the upper arm; leads to the axillary vein

cerebrovascular accident (CVA)

blockage of blood flow to the brain; also called a stroke

circle of Willis

(also, arterial circle) anastomosis located at the base of the brain that ensures continual blood supply; formed from branches of the internal carotid and vertebral arteries; supplies blood to the brain

common carotid artery

right common carotid artery arises from the brachiocephalic artery, and the left common carotid arises from the aortic arch; gives rise to the

external and internal carotid arteries; supplies the respective sides of the head and neck

common hepatic artery

branch of the celiac trunk that forms the hepatic artery, the right gastric artery, and the cystic artery

common iliac artery

branch of the aorta that leads to the internal and external iliac arteries

common iliac vein

one of a pair of veins that flows into the inferior vena cava at the level of L5; the left common iliac vein drains the sacral region; divides into external and internal iliac veins near the inferior portion of the sacroiliac joint

cystic artery

branch of the common hepatic artery; supplies blood to the gall bladder

deep femoral artery

branch of the femoral artery; gives rise to the lateral circumflex arteries

deep femoral vein

drains blood from the deeper portions of the thigh and leads to the femoral vein

descending aorta

portion of the aorta that continues downward past the end of the aortic arch; subdivided into the thoracic aorta and the abdominal aorta

digital arteries

formed from the superficial and deep palmar arches; supply blood to the digits

digital veins

drain the digits and feed into the palmar arches of the hand and dorsal venous arch of the foot

dorsal arch

(also, arcuate arch) formed from the anastomosis of the dorsalis pedis artery and medial and plantar arteries; branches supply the distal portions of the foot and digits

dorsal venous arch

drains blood from digital veins and vessels on the superior surface of the foot

dorsalis pedis artery

forms from the anterior tibial artery; branches repeatedly to supply blood to the tarsal and dorsal regions of the foot

esophageal artery

branch of the thoracic aorta; supplies blood to the esophagus

esophageal vein

drains the inferior portions of the esophagus and leads to the azygos vein

external carotid artery

arises from the common carotid artery; supplies blood to numerous structures within the face, lower jaw, neck, esophagus, and larynx

external iliac artery

branch of the common iliac artery that leaves the body cavity and becomes a femoral artery; supplies blood to the lower limbs

external iliac vein

formed when the femoral vein passes into the body cavity; drains the legs and leads to the common iliac vein

external jugular vein

one of a pair of major veins located in the superficial neck region that drains blood from the more superficial portions of the head, scalp, and

cranial regions, and leads to the subclavian vein

femoral artery

continuation of the external iliac artery after it passes through the body cavity; divides into several smaller branches, the lateral deep femoral artery, and the genicular artery; becomes the popliteal artery as it passes posterior to the knee

femoral circumflex vein

forms a loop around the femur just inferior to the trochanters; drains blood from the areas around the head and neck of the femur; leads to the femoral vein

femoral vein

drains the upper leg; receives blood from the great saphenous vein, the deep femoral vein, and the femoral circumflex vein; becomes the external iliac vein when it crosses the body wall

fibular vein

drains the muscles and integument near the fibula and leads to the popliteal vein

genicular artery

branch of the femoral artery; supplies blood to the region of the knee

gonadal artery

branch of the abdominal aorta; supplies blood to the gonads or reproductive organs; also described as ovarian arteries or testicular arteries, depending upon the sex of the individual

gonadal vein

generic term for a vein draining a reproductive organ; may be either an ovarian vein or a testicular vein, depending on the sex of the individual

great cerebral vein

receives most of the smaller vessels from the inferior cerebral veins and leads to the straight sinus

great saphenous vein

prominent surface vessel located on the medial surface of the leg and thigh; drains the superficial portions of these areas and leads to the femoral vein

hemiazygos vein

smaller vein complementary to the azygos vein; drains the esophageal veins from the esophagus and the left intercostal veins, and leads to the brachiocephalic vein via the superior intercostal vein

hepatic artery proper

branch of the common hepatic artery; supplies systemic blood to the liver

hepatic portal system

specialized circulatory pathway that carries blood from digestive organs to the liver for processing before being sent to the systemic circulation

hepatic vein

drains systemic blood from the liver and flows into the inferior vena cava

inferior mesenteric artery

branch of the abdominal aorta; supplies blood to the distal segment of the large intestine and rectum

inferior phrenic artery

branch of the abdominal aorta; supplies blood to the inferior surface of the diaphragm

inferior vena cava

large systemic vein that drains blood from areas largely inferior to the diaphragm; empties into the right atrium

intercostal artery

branch of the thoracic aorta; supplies blood to the muscles of the thoracic cavity and vertebral column

intercostal vein

drains the muscles of the thoracic wall and leads to the azygos vein

internal carotid artery

arises from the common carotid artery and begins with the carotid sinus; goes through the carotid canal of the temporal bone to the base of the brain; combines with branches of the vertebral artery forming the arterial circle; supplies blood to the brain

internal iliac artery

branch from the common iliac arteries; supplies blood to the urinary bladder, walls of the pelvis, external genitalia, and the medial portion of the femoral region; in females, also provide blood to the uterus and vagina

internal iliac vein

drains the pelvic organs and integument; formed from several smaller veins in the region; leads to the common iliac vein

internal jugular vein

one of a pair of major veins located in the neck region that passes through the jugular foramen and canal, flows parallel to the common carotid artery that is more or less its counterpart; primarily drains blood from the brain, receives the superficial facial vein, and empties into the subclavian vein

internal thoracic artery

(also, mammary artery) arises from the subclavian artery; supplies blood to the thymus, pericardium of the heart, and the anterior chest wall

internal thoracic vein

(also, internal mammary vein) drains the anterior surface of the chest wall and leads to the brachiocephalic vein

lateral circumflex artery

branch of the deep femoral artery; supplies blood to the deep muscles of the thigh and the ventral and lateral regions of the integument

lateral plantar artery

arises from the bifurcation of the posterior tibial arteries; supplies blood to the lateral plantar surfaces of the foot

left gastric artery

branch of the celiac trunk; supplies blood to the stomach

lumbar arteries

branches of the abdominal aorta; supply blood to the lumbar region, the abdominal wall, and spinal cord

lumbar veins

drain the lumbar portion of the abdominal wall and spinal cord; the superior lumbar veins drain into the azygos vein on the right or the hemiazygos vein on the left; blood from these vessels is returned to the superior vena cava rather than the inferior vena cava

maxillary vein

drains blood from the maxillary region and leads to the external jugular vein

medial plantar artery

arises from the bifurcation of the posterior tibial arteries; supplies blood to the medial plantar surfaces of the foot

median antebrachial vein

vein that parallels the ulnar vein but is more medial in location; intertwines with the palmar venous arches

median cubital vein

superficial vessel located in the antecubital region that links the cephalic vein to the basilic vein in the form of a v; a frequent site for a blood draw

median sacral artery

continuation of the aorta into the sacrum

mediastinal artery

branch of the thoracic aorta; supplies blood to the mediastinum

middle cerebral artery

another branch of the internal carotid artery; supplies blood to the temporal and parietal lobes of the cerebrum

middle sacral vein

drains the sacral region and leads to the left common iliac vein

occipital sinus

enlarged vein that drains the occipital region near the falx cerebelli and flows into the left and right transverse sinuses, and also into the vertebral veins

ophthalmic artery

branch of the internal carotid artery; supplies blood to the eyes

ovarian artery

branch of the abdominal aorta; supplies blood to the ovary, uterine (Fallopian) tube, and uterus

ovarian vein

drains the ovary; the right ovarian vein leads to the inferior vena cava and the left ovarian vein leads to the left renal vein

palmar arches

superficial and deep arches formed from anastomoses of the radial and ulnar arteries; supply blood to the hand and digital arteries

palmar venous arches

drain the hand and digits, and feed into the radial and ulnar veins

parietal branches

(also, somatic branches) group of arterial branches of the thoracic aorta; includes those that supply blood to the thoracic cavity, vertebral column, and the superior surface of the diaphragm

pericardial artery

branch of the thoracic aorta; supplies blood to the pericardium

petrosal sinus

enlarged vein that receives blood from the cavernous sinus and flows into the internal jugular vein

phrenic vein

drains the diaphragm; the right phrenic vein flows into the inferior vena cava and the left phrenic vein leads to the left renal vein

plantar arch

formed from the anastomosis of the dorsalis pedis artery and medial and plantar arteries; branches supply the distal portions of the foot and digits

plantar veins

drain the foot and lead to the plantar venous arch

plantar venous arch

formed from the plantar veins; leads to the anterior and posterior tibial veins through anastomoses

popliteal artery

continuation of the femoral artery posterior to the knee; branches into the anterior and posterior tibial arteries

popliteal vein

continuation of the femoral vein behind the knee; drains the region behind the knee and forms from the fusion of the fibular and anterior and posterior tibial veins

posterior cerebral artery

branch of the basilar artery that forms a portion of the posterior segment of the arterial circle; supplies blood to the posterior portion of the cerebrum and brain stem

posterior communicating artery

branch of the posterior cerebral artery that forms part of the posterior portion of the arterial circle; supplies blood to the brain

posterior tibial artery

branch from the popliteal artery that gives rise to the fibular or peroneal artery; supplies blood to the posterior tibial region

posterior tibial vein

forms from the dorsal venous arch; drains the area near the posterior surface of the tibia and leads to the popliteal vein

pulmonary artery

one of two branches, left and right, that divides off from the pulmonary trunk and leads to smaller arterioles and eventually to the pulmonary capillaries

pulmonary circuit

system of blood vessels that provide gas exchange via a network of arteries, veins, and capillaries that run from the heart, through the body, and back to the lungs

pulmonary trunk

single large vessel exiting the right ventricle that divides to form the right and left pulmonary arteries

pulmonary veins

two sets of paired vessels, one pair on each side, that are formed from the small venules leading away from the pulmonary capillaries that flow into the left atrium

radial artery

formed at the bifurcation of the brachial artery; parallels the radius; gives off smaller branches until it reaches the carpal region where it fuses with the ulnar artery to form the superficial and deep palmar arches; supplies blood to the lower arm and carpal region

radial vein

parallels the radius and radial artery; arises from the palmar venous arches and leads to the brachial vein

renal artery

branch of the abdominal aorta; supplies each kidney

renal vein

largest vein entering the inferior vena cava; drains the kidneys and leads to the inferior vena cava

right gastric artery

branch of the common hepatic artery; supplies blood to the stomach

sigmoid sinuses

enlarged veins that receive blood from the transverse sinuses; flow through the jugular foramen and into the internal jugular vein

small saphenous vein

located on the lateral surface of the leg; drains blood from the superficial regions of the lower leg and foot, and leads to the popliteal vein

splenic artery

branch of the celiac trunk; supplies blood to the spleen

straight sinus

enlarged vein that drains blood from the brain; receives most of the blood from the great cerebral vein and flows into the left or right transverse sinus

subclavian artery

right subclavian arises from the brachiocephalic artery, whereas the left subclavian artery arises from the aortic arch; gives rise to the internal thoracic, vertebral, and thyrocervical arteries; supplies blood to the arms, chest, shoulders, back, and central nervous system

subclavian vein

located deep in the thoracic cavity; becomes the axillary vein as it enters the axillary region; drains the axillary and smaller local veins near the scapular region; leads to the brachiocephalic vein

subscapular vein

drains blood from the subscapular region and leads to the axillary vein

superior mesenteric artery

branch of the abdominal aorta; supplies blood to the small intestine (duodenum, jejunum, and ileum), the pancreas, and a majority of the large intestine

superior phrenic artery

branch of the thoracic aorta; supplies blood to the superior surface of the diaphragm

superior sagittal sinus

enlarged vein located midsagittally between the meningeal and periosteal layers of the dura mater within the falx cerebri; receives most of the blood drained from the superior surface of the cerebrum and leads to the inferior jugular vein and the vertebral vein

superior vena cava

large systemic vein; drains blood from most areas superior to the diaphragm; empties into the right atrium

temporal vein

drains blood from the temporal region and leads to the external jugular vein

testicular artery

branch of the abdominal aorta; will ultimately travel outside the body cavity to the testes and form one component of the spermatic cord

testicular vein

drains the testes and forms part of the spermatic cord; the right testicular vein empties directly into the inferior vena cava and the left testicular vein empties into the left renal vein

thoracic aorta

portion of the descending aorta superior to the aortic hiatus

thyrocervical artery

arises from the subclavian artery; supplies blood to the thyroid, the cervical region, the upper back, and shoulder

transient ischemic attack (TIA)

temporary loss of neurological function caused by a brief interruption in blood flow; also known as a mini-stroke

transverse sinuses

pair of enlarged veins near the lambdoid suture that drain the occipital, sagittal, and straight sinuses, and leads to the sigmoid sinuses

trunk

large vessel that gives rise to smaller vessels

ulnar artery

formed at the bifurcation of the brachial artery; parallels the ulna; gives off smaller branches until it reaches the carpal region where it fuses with the radial artery to form the superficial and deep palmar arches; supplies blood to the lower arm and carpal region

ulnar vein

parallels the ulna and ulnar artery; arises from the palmar venous arches and leads to the brachial vein

vertebral artery

arises from the subclavian artery and passes through the vertebral foramen through the foramen magnum to the brain; joins with the internal carotid artery to form the arterial circle; supplies blood to the brain and spinal cord

vertebral vein

arises from the base of the brain and the cervical region of the spinal cord; passes through the intervertebral foramina in the cervical vertebrae; drains smaller veins from the cranium, spinal cord, and

vertebrae, and leads to the brachiocephalic vein; counterpart of the vertebral artery

visceral branches

branches of the descending aorta that supply blood to the viscera

Introduction

class="introduction"

Mountain Climbers

The thin air at high elevations can strain the human respiratory system.

(credit:
“bortescristian”/flickr.com
)



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- List the structures of the respiratory system
- List the major functions of the respiratory system
- Outline the forces that allow for air movement into and out of the lungs
- Outline the process of gas exchange
- Summarize the process of oxygen and carbon dioxide transport within the respiratory system
- Create a flow chart illustrating how respiration is controlled
- Discuss how the respiratory system responds to exercise
- Describe the development of the respiratory system in the embryo

Hold your breath. Really! See how long you can hold your breath as you continue reading...How long can you do it? Chances are you are feeling uncomfortable already. A typical human cannot survive without breathing for more than 3 minutes, and even if you wanted to hold your breath longer, your autonomic nervous system would take control. This is because every cell in the body needs to run the oxidative stages of cellular respiration, the process by which energy is produced in the form of adenosine triphosphate (ATP). For oxidative phosphorylation to occur, oxygen is used as a reactant and carbon dioxide is released as a waste product. You may be surprised to learn that although oxygen is a critical need for cells, it is actually the accumulation of carbon dioxide that primarily drives your need to breathe. Carbon dioxide is exhaled and oxygen is inhaled through the respiratory system, which includes muscles to move air into and out of the lungs, passageways through which air moves, and microscopic gas exchange surfaces covered by capillaries. The circulatory system transports gases from the lungs to tissues throughout the body and vice versa. A variety of diseases can affect the respiratory system, such as asthma, emphysema, chronic obstruction pulmonary disorder (COPD), and lung cancer. All of these conditions affect the gas exchange process and result in labored breathing and other difficulties.

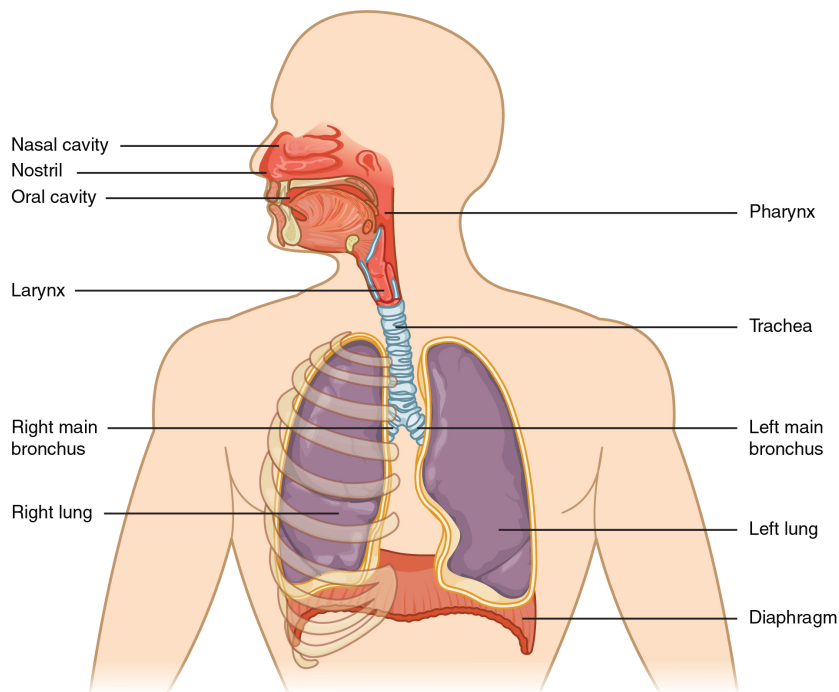
Organs and Structures of the Respiratory System

By the end of this section, you will be able to:

- List the structures that make up the respiratory system
- Describe how the respiratory system processes oxygen and CO₂
- Compare and contrast the functions of upper respiratory tract with the lower respiratory tract

The major organs of the respiratory system function primarily to provide oxygen to body tissues for cellular respiration, remove the waste product carbon dioxide, and help to maintain acid-base balance. Portions of the respiratory system are also used for non-vital functions, such as sensing odors, speech production, and for straining, such as during childbirth or coughing ([link](#)).

Major Respiratory Structures



The major respiratory structures span the nasal cavity to the diaphragm.

Functionally, the respiratory system can be divided into a conducting zone and a respiratory zone. The **conducting zone** of the respiratory system includes the organs and structures not directly involved in gas exchange. The gas exchange occurs in the **respiratory zone**.

Conducting Zone

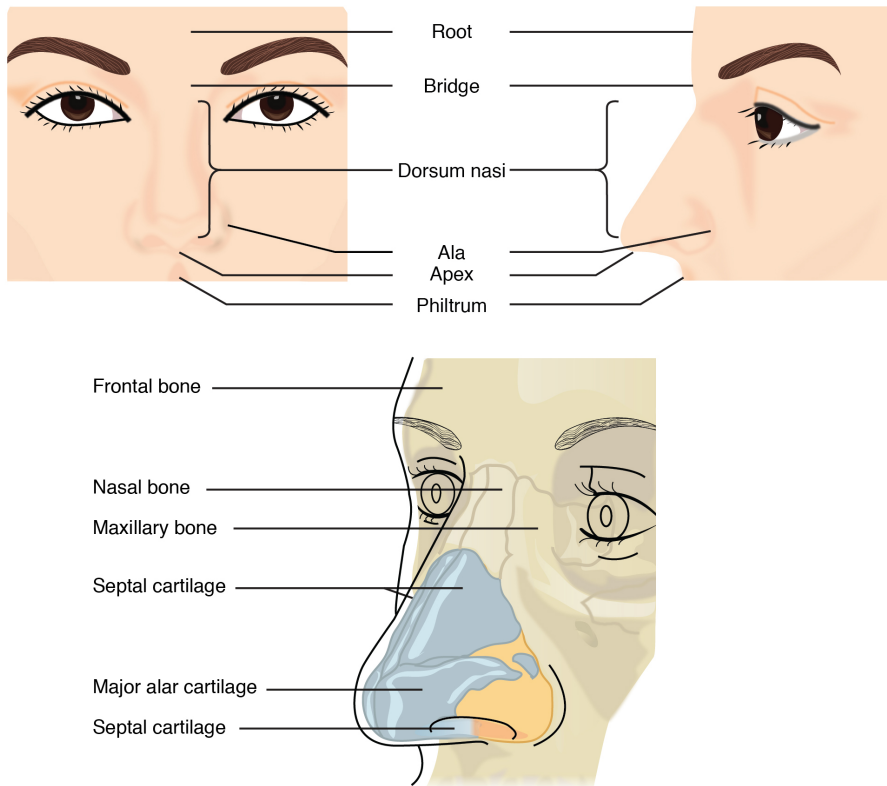
The major functions of the conducting zone are to provide a route for incoming and outgoing air, remove debris and pathogens from the incoming air, and warm and humidify the incoming air. Several structures within the conducting zone perform other functions as well. The epithelium of the nasal passages, for example, is essential to sensing odors, and the bronchial epithelium that lines the lungs can metabolize some airborne carcinogens.

The Nose and its Adjacent Structures

The major entrance and exit for the respiratory system is through the nose. When discussing the nose, it is helpful to divide it into two major sections: the external nose, and the nasal cavity or internal nose.

The **external nose** consists of the surface and skeletal structures that result in the outward appearance of the nose and contribute to its numerous functions ([\[link\]](#)). The **root** is the region of the nose located between the eyebrows. The **bridge** is the part of the nose that connects the root to the rest of the nose. The **dorsum nasi** is the length of the nose. The **apex** is the tip of the nose. On either side of the apex, the nostrils are formed by the alae (singular = ala). An **ala** is a cartilaginous structure that forms the lateral side of each **naris** (plural = nares), or nostril opening. The **philtrum** is the concave surface that connects the apex of the nose to the upper lip.

Nose



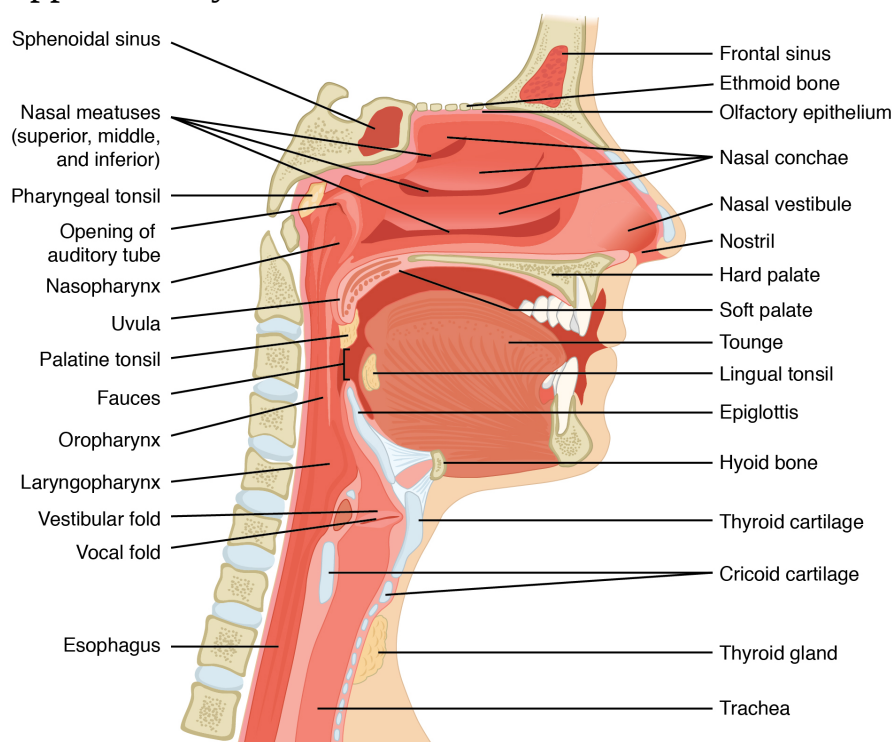
This illustration shows features of the external nose (top) and skeletal features of the nose (bottom).

Underneath the thin skin of the nose are its skeletal features (see [\[link\]](#), lower illustration). While the root and bridge of the nose consist of bone, the protruding portion of the nose is composed of cartilage. As a result, when looking at a skull, the nose is missing. The **nasal bone** is one of a pair of bones that lies under the root and bridge of the nose. The nasal bone articulates superiorly with the frontal bone and laterally with the maxillary bones. Septal cartilage is flexible hyaline cartilage connected to the nasal bone, forming the dorsum nasi. The **alar cartilage** consists of the apex of the nose; it surrounds the naris.

The nares open into the nasal cavity, which is separated into left and right sections by the nasal septum ([\[link\]](#)). The **nasal septum** is formed anteriorly by a portion of the septal cartilage (the flexible portion you can

touch with your fingers) and posteriorly by the perpendicular plate of the ethmoid bone (a cranial bone located just posterior to the nasal bones) and the thin vomer bones (whose name refers to its plough shape). Each lateral wall of the nasal cavity has three bony projections, called the superior, middle, and inferior nasal conchae. The inferior conchae are separate bones, whereas the superior and middle conchae are portions of the ethmoid bone. Conchae serve to increase the surface area of the nasal cavity and to disrupt the flow of air as it enters the nose, causing air to bounce along the epithelium, where it is cleaned and warmed. The conchae and **meatuses** also conserve water and prevent dehydration of the nasal epithelium by trapping water during exhalation. The floor of the nasal cavity is composed of the palate. The hard palate at the anterior region of the nasal cavity is composed of bone. The soft palate at the posterior portion of the nasal cavity consists of muscle tissue. Air exits the nasal cavities via the internal nares and moves into the pharynx.

Upper Airway



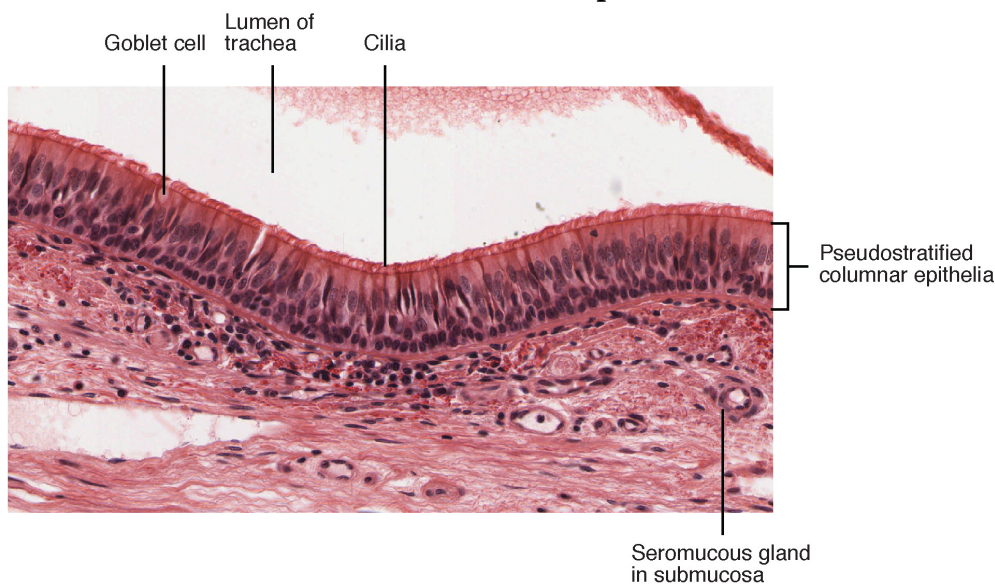
Several bones that help form the walls of the nasal cavity have air-containing spaces called the paranasal sinuses, which serve to warm and humidify incoming air. Sinuses are lined with a mucosa. Each **paranasal sinus** is named for its associated bone: frontal sinus, maxillary sinus,

sphenoidal sinus, and ethmoidal sinus. The sinuses produce mucus and lighten the weight of the skull.

The nares and anterior portion of the nasal cavities are lined with mucous membranes, containing sebaceous glands and hair follicles that serve to prevent the passage of large debris, such as dirt, through the nasal cavity. An olfactory epithelium used to detect odors is found deeper in the nasal cavity.

The conchae, meatuses, and paranasal sinuses are lined by **respiratory epithelium** composed of pseudostratified ciliated columnar epithelium ([\[link\]](#)). The epithelium contains goblet cells, one of the specialized, columnar epithelial cells that produce mucus to trap debris. The cilia of the respiratory epithelium help remove the mucus and debris from the nasal cavity with a constant beating motion, sweeping materials towards the throat to be swallowed. Interestingly, cold air slows the movement of the cilia, resulting in accumulation of mucus that may in turn lead to a runny nose during cold weather. This moist epithelium functions to warm and humidify incoming air. Capillaries located just beneath the nasal epithelium warm the air by convection. Serous and mucus-producing cells also secrete the lysozyme enzyme and proteins called defensins, which have antibacterial properties. Immune cells that patrol the connective tissue deep to the respiratory epithelium provide additional protection.

Pseudostratified Ciliated Columnar Epithelium



Respiratory epithelium is pseudostratified ciliated columnar epithelium. Seromucous glands provide lubricating mucus. LM \times 680. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:

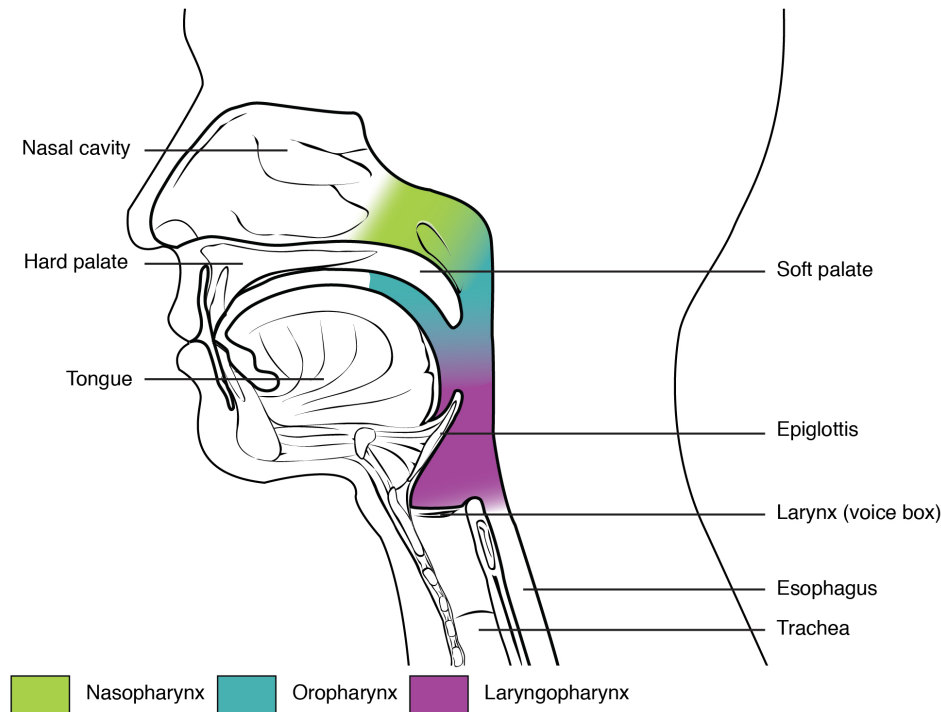


View the [University of Michigan WebScope](#) to explore the tissue sample in greater detail.

Pharynx

The **pharynx** is a tube formed by skeletal muscle and lined by mucous membrane that is continuous with that of the nasal cavities (see [\[link\]](#)). The pharynx is divided into three major regions: the nasopharynx, the oropharynx, and the laryngopharynx ([\[link\]](#)).

Divisions of the Pharynx



The pharynx is divided into three regions: the nasopharynx, the oropharynx, and the laryngopharynx.

The **nasopharynx** is flanked by the conchae of the nasal cavity, and it serves only as an airway. At the top of the nasopharynx are the pharyngeal tonsils. A **pharyngeal tonsil**, also called an adenoid, is an aggregate of lymphoid reticular tissue similar to a lymph node that lies at the superior portion of the nasopharynx. The function of the pharyngeal tonsil is not well understood, but it contains a rich supply of lymphocytes and is covered with ciliated epithelium that traps and destroys invading pathogens that enter during inhalation. The pharyngeal tonsils are large in children, but interestingly, tend to regress with age and may even disappear. The uvula is a small bulbous, teardrop-shaped structure located at the apex of the soft palate. Both the uvula and soft palate move like a pendulum during swallowing, swinging upward to close off the nasopharynx to prevent ingested materials from entering the nasal cavity. In addition, auditory

(Eustachian) tubes that connect to each middle ear cavity open into the nasopharynx. This connection is why colds often lead to ear infections.

The **oropharynx** is a passageway for both air and food. The oropharynx is bordered superiorly by the nasopharynx and anteriorly by the oral cavity. The **fauces** is the opening at the connection between the oral cavity and the oropharynx. As the nasopharynx becomes the oropharynx, the epithelium changes from pseudostratified ciliated columnar epithelium to stratified squamous epithelium. The oropharynx contains two distinct sets of tonsils, the palatine and lingual tonsils. A **palatine tonsil** is one of a pair of structures located laterally in the oropharynx in the area of the fauces. The **lingual tonsil** is located at the base of the tongue. Similar to the pharyngeal tonsil, the palatine and lingual tonsils are composed of lymphoid tissue, and trap and destroy pathogens entering the body through the oral or nasal cavities.

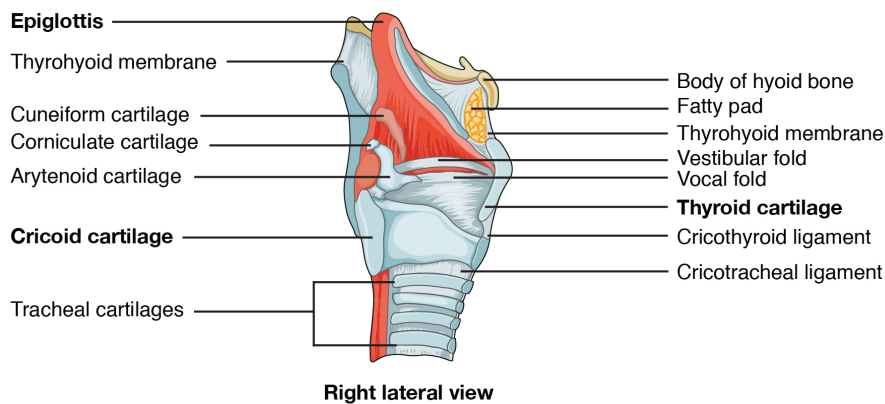
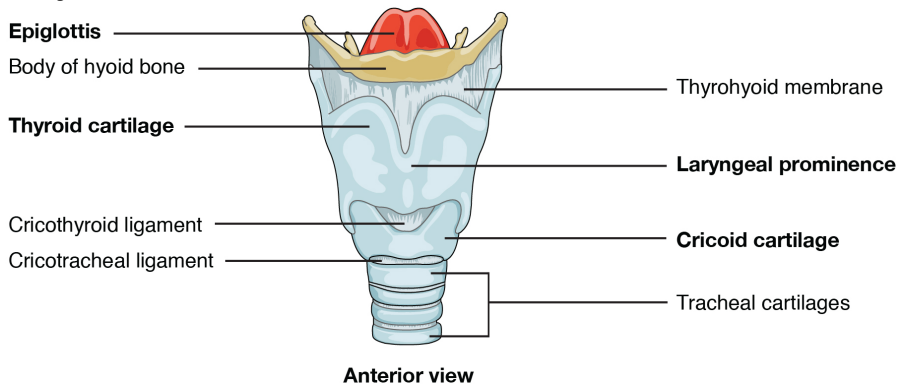
The **laryngopharynx** is inferior to the oropharynx and posterior to the larynx. It continues the route for ingested material and air until its inferior end, where the digestive and respiratory systems diverge. The stratified squamous epithelium of the oropharynx is continuous with the laryngopharynx. Anteriorly, the laryngopharynx opens into the larynx, whereas posteriorly, it enters the esophagus.

Larynx

The **larynx** is a cartilaginous structure inferior to the laryngopharynx that connects the pharynx to the trachea and helps regulate the volume of air that enters and leaves the lungs ([\[link\]](#)). The structure of the larynx is formed by several pieces of cartilage. Three large cartilage pieces—the thyroid cartilage (anterior), epiglottis (superior), and cricoid cartilage (inferior)—form the major structure of the larynx. The **thyroid cartilage** is the largest piece of cartilage that makes up the larynx. The thyroid cartilage consists of the **laryngeal prominence**, or “Adam’s apple,” which tends to be more prominent in males. The thick **cricoid cartilage** forms a ring, with a wide posterior region and a thinner anterior region. Three smaller, paired cartilages—the arytenoids, corniculates, and cuneiforms—attach to the

epiglottis and the vocal cords and muscle that help move the vocal cords to produce speech.

Larynx

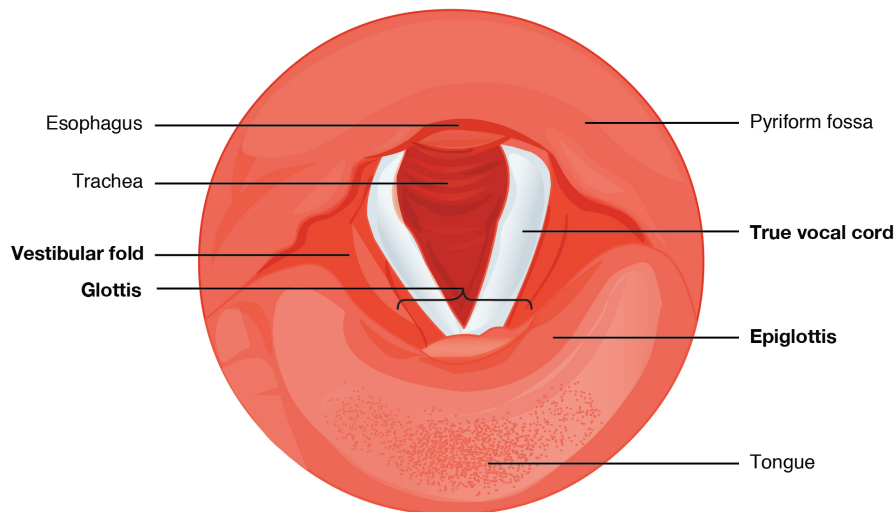


The larynx extends from the laryngopharynx and the hyoid bone to the trachea.

The **epiglottis**, attached to the thyroid cartilage, is a very flexible piece of elastic cartilage that covers the opening of the trachea (see [\[link\]](#)). When in the “closed” position, the unattached end of the epiglottis rests on the glottis. The **glottis** is composed of the vestibular folds, the true vocal cords, and the space between these folds ([\[link\]](#)). A **vestibular fold**, or false vocal cord, is one of a pair of folded sections of mucous membrane. A **true vocal cord** is one of the white, membranous folds attached by muscle to the thyroid and arytenoid cartilages of the larynx on their outer edges. The inner edges of the true vocal cords are free, allowing oscillation to produce sound. The size of the membranous folds of the true vocal cords differs

between individuals, producing voices with different pitch ranges. Folds in males tend to be larger than those in females, which create a deeper voice. The act of swallowing causes the pharynx and larynx to lift upward, allowing the pharynx to expand and the epiglottis of the larynx to swing downward, closing the opening to the trachea. These movements produce a larger area for food to pass through, while preventing food and beverages from entering the trachea.

Vocal Cords



The true vocal cords and vestibular folds of the larynx are viewed inferiorly from the laryngopharynx.

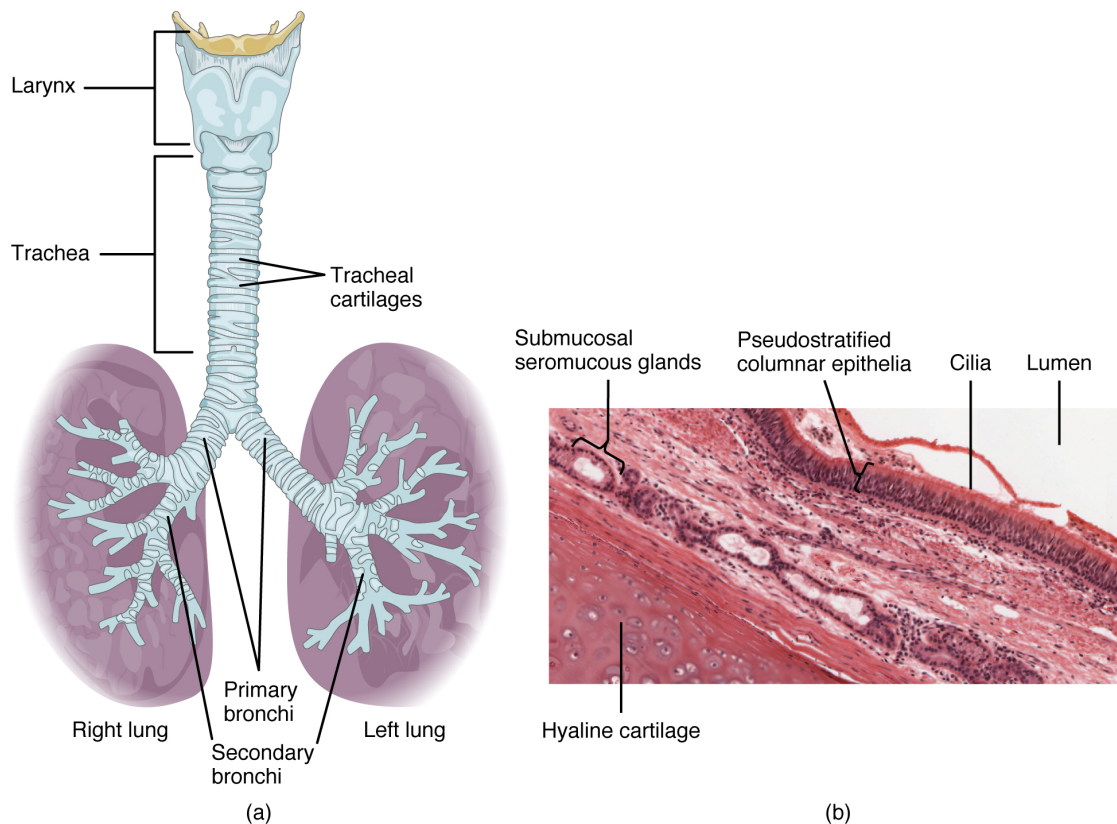
Continuous with the laryngopharynx, the superior portion of the larynx is lined with stratified squamous epithelium, transitioning into pseudostratified ciliated columnar epithelium that contains goblet cells. Similar to the nasal cavity and nasopharynx, this specialized epithelium produces mucus to trap debris and pathogens as they enter the trachea. The cilia beat the mucus upward towards the laryngopharynx, where it can be swallowed down the esophagus.

Trachea

The trachea (windpipe) extends from the larynx toward the lungs ([link](#))**a**. The **trachea** is formed by 16 to 20 stacked, C-shaped pieces of hyaline cartilage that are connected by dense connective tissue. The **trachealis muscle** and elastic connective tissue together form the **fibroelastic membrane**, a flexible membrane that closes the posterior surface of the trachea, connecting the C-shaped cartilages. The fibroelastic membrane allows the trachea to stretch and expand slightly during inhalation and exhalation, whereas the rings of cartilage provide structural support and prevent the trachea from collapsing. In addition, the trachealis muscle can be contracted to force air through the trachea during exhalation. The trachea is lined with pseudostratified ciliated columnar epithelium, which is continuous with the larynx. The esophagus borders the trachea posteriorly.

Trachea

(a) The tracheal tube is formed by stacked, C-shaped pieces of hyaline cartilage. (b) The layer visible in this cross-section of tracheal wall tissue between the hyaline cartilage and the lumen of the trachea is the mucosa, which is composed of pseudostratified ciliated columnar epithelium that contains goblet cells. LM \times 1220. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



Bronchial Tree

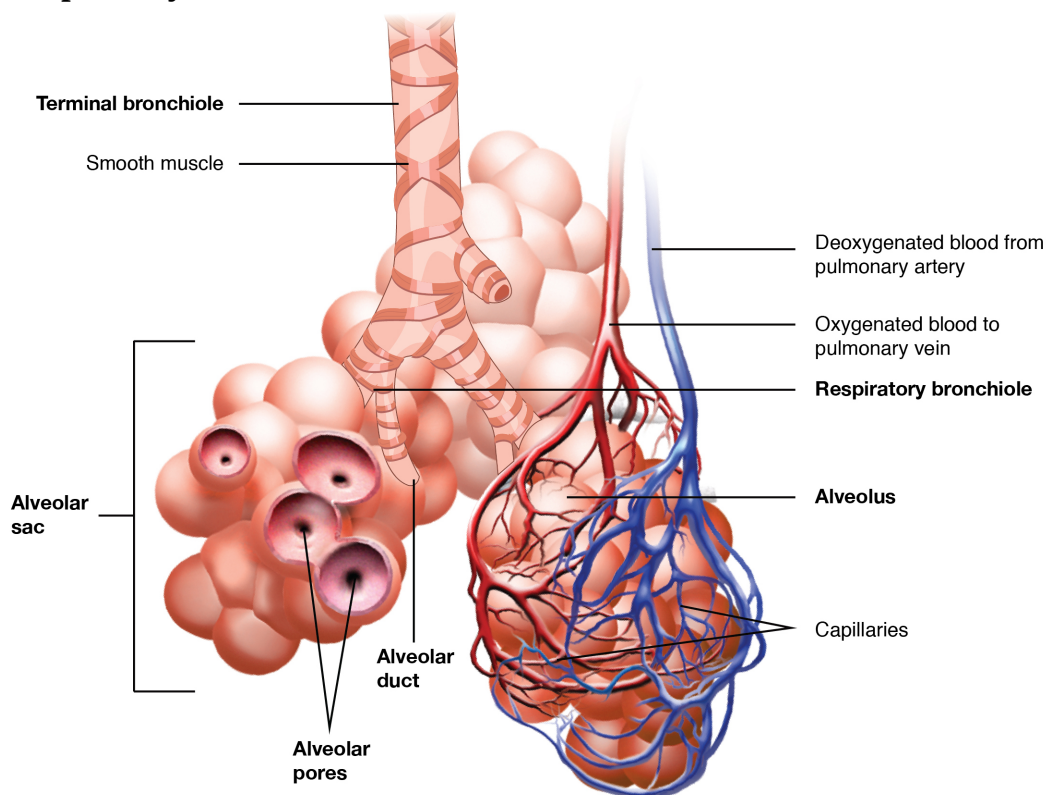
The trachea branches into the right and left primary **bronchi** at the carina. These bronchi are also lined by pseudostratified ciliated columnar epithelium containing mucus-producing goblet cells ([link](#)**b**). The carina is a raised structure that contains specialized nervous tissue that induces violent coughing if a foreign body, such as food, is present. Rings of cartilage, similar to those of the trachea, support the structure of the bronchi and prevent their collapse. The primary bronchi enter the lungs at the hilum, a concave region where blood vessels, lymphatic vessels, and nerves also enter the lungs. The bronchi continue to branch into bronchial a tree. A **bronchial tree** (or respiratory tree) is the collective term used for these multiple-branched bronchi. The main function of the bronchi, like other conducting zone structures, is to provide a passageway for air to move into and out of each lung. In addition, the mucous membrane traps debris and pathogens.

A **bronchiole** branches from the tertiary bronchi. Bronchioles, which are about 1 mm in diameter, further branch until they become the tiny terminal bronchioles, which lead to the structures of gas exchange. There are more than 1000 terminal bronchioles in each lung. The muscular walls of the bronchioles do not contain cartilage like those of the bronchi. This muscular wall can change the size of the tubing to increase or decrease airflow through the tube.

Respiratory Zone

In contrast to the conducting zone, the respiratory zone includes structures that are directly involved in gas exchange. The respiratory zone begins where the terminal bronchioles join a **respiratory bronchiole**, the smallest type of bronchiole ([\[link\]](#)), which then leads to an alveolar duct, opening into a cluster of alveoli.

Respiratory Zone



Bronchioles lead to alveolar sacs in the respiratory zone, where gas exchange occurs.

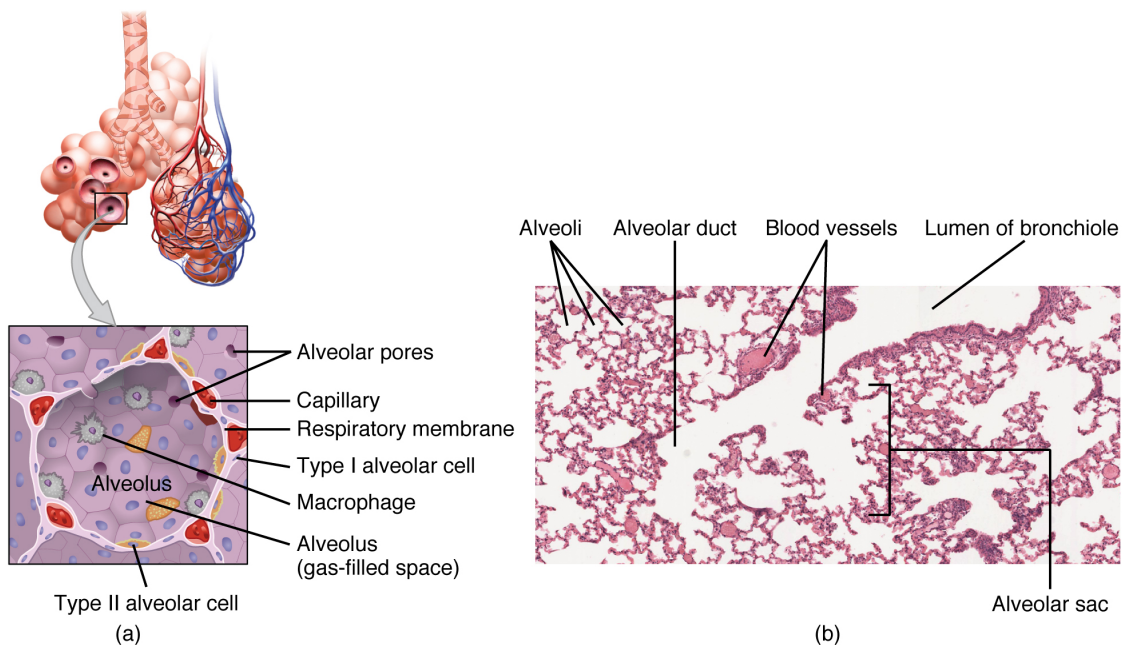
Alveoli

An **alveolar duct** is a tube composed of smooth muscle and connective tissue, which opens into a cluster of alveoli. An **alveolus** is one of the many small, grape-like sacs that are attached to the alveolar ducts.

An **alveolar sac** is a cluster of many individual alveoli that are responsible for gas exchange. An alveolus is approximately 200 μm in diameter with elastic walls that allow the alveolus to stretch during air intake, which greatly increases the surface area available for gas exchange. Alveoli are connected to their neighbors by **alveolar pores**, which help maintain equal air pressure throughout the alveoli and lung ([link](#)).

Structures of the Respiratory Zone

- (a) The alveolus is responsible for gas exchange. (b) A micrograph shows the alveolar structures within lung tissue. LM $\times 178$.
(Micrograph provided by the Regents of University of Michigan Medical School © 2012)



The alveolar wall consists of three major cell types: type I alveolar cells, type II alveolar cells, and alveolar macrophages. A **type I alveolar cell** is a squamous epithelial cell of the alveoli, which constitute up to 97 percent of the alveolar surface area. These cells are about 25 nm thick and are highly permeable to gases. A **type II alveolar cell** is interspersed among the type I cells and secretes **pulmonary surfactant**, a substance composed of phospholipids and proteins that reduces the surface tension of the alveoli. Roaming around the alveolar wall is the **alveolar macrophage**, a phagocytic cell of the immune system that removes debris and pathogens that have reached the alveoli.

The simple squamous epithelium formed by type I alveolar cells is attached to a thin, elastic basement membrane. This epithelium is extremely thin and borders the endothelial membrane of capillaries. Taken together, the alveoli and capillary membranes form a **respiratory membrane** that is approximately 0.5 mm thick. The respiratory membrane allows gases to cross by simple diffusion, allowing oxygen to be picked up by the blood for transport and CO₂ to be released into the air of the alveoli.

Note:

Diseases of the...

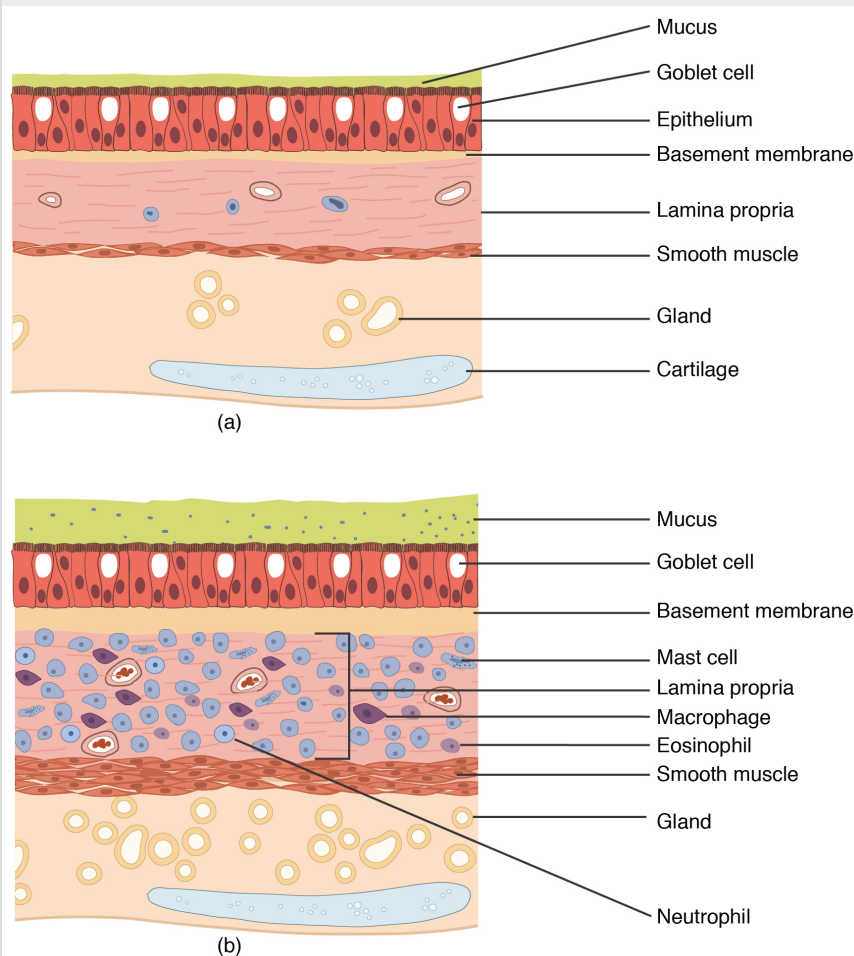
Respiratory System: Asthma

Asthma is common condition that affects the lungs in both adults and children. Approximately 8.2 percent of adults (18.7 million) and 9.4 percent of children (7 million) in the United States suffer from asthma. In addition, asthma is the most frequent cause of hospitalization in children. Asthma is a chronic disease characterized by inflammation and edema of the airway, and bronchospasms (that is, constriction of the bronchioles), which can inhibit air from entering the lungs. In addition, excessive mucus secretion can occur, which further contributes to airway occlusion ([\[link\]](#)). Cells of the immune system, such as eosinophils and mononuclear cells, may also be involved in infiltrating the walls of the bronchi and bronchioles.

Bronchospasms occur periodically and lead to an “asthma attack.” An attack may be triggered by environmental factors such as dust, pollen, pet

hair, or dander, changes in the weather, mold, tobacco smoke, and respiratory infections, or by exercise and stress.

Normal and Bronchial Asthma Tissues



(a) Normal lung tissue does not have the characteristics of lung tissue during (b) an asthma attack, which include thickened mucosa, increased mucus-producing goblet cells, and eosinophil infiltrates.

Symptoms of an asthma attack involve coughing, shortness of breath, wheezing, and tightness of the chest. Symptoms of a severe asthma attack that requires immediate medical attention would include difficulty breathing that results in blue (cyanotic) lips or face, confusion, drowsiness, a rapid pulse, sweating, and severe anxiety. The severity of the condition,

frequency of attacks, and identified triggers influence the type of medication that an individual may require. Longer-term treatments are used for those with more severe asthma. Short-term, fast-acting drugs that are used to treat an asthma attack are typically administered via an inhaler. For young children or individuals who have difficulty using an inhaler, asthma medications can be administered via a nebulizer. In many cases, the underlying cause of the condition is unknown. However, recent research has demonstrated that certain viruses, such as human rhinovirus C (HRVC), and the bacteria *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* that are contracted in infancy or early childhood, may contribute to the development of many cases of asthma.

Note:



Visit this [site](#) to learn more about what happens during an asthma attack. What are the three changes that occur inside the airways during an asthma attack?

Chapter Review

The respiratory system is responsible for obtaining oxygen and getting rid of carbon dioxide, and aiding in speech production and in sensing odors. From a functional perspective, the respiratory system can be divided into two major areas: the conducting zone and the respiratory zone. The conducting zone consists of all of the structures that provide passageways for air to travel into and out of the lungs: the nasal cavity, pharynx, trachea, bronchi, and most bronchioles. The nasal passages contain the conchae and

meatuses that expand the surface area of the cavity, which helps to warm and humidify incoming air, while removing debris and pathogens. The pharynx is composed of three major sections: the nasopharynx, which is continuous with the nasal cavity; the oropharynx, which borders the nasopharynx and the oral cavity; and the laryngopharynx, which borders the oropharynx, trachea, and esophagus. The respiratory zone includes the structures of the lung that are directly involved in gas exchange: the terminal bronchioles and alveoli.

The lining of the conducting zone is composed mostly of pseudostratified ciliated columnar epithelium with goblet cells. The mucus traps pathogens and debris, whereas beating cilia move the mucus superiorly toward the throat, where it is swallowed. As the bronchioles become smaller and smaller, and nearer the alveoli, the epithelium thins and is simple squamous epithelium in the alveoli. The endothelium of the surrounding capillaries, together with the alveolar epithelium, forms the respiratory membrane. This is a blood-air barrier through which gas exchange occurs by simple diffusion.

Interactive Link Questions

Exercise:

Problem:

Visit this [site](#) to learn more about what happens during an asthma attack. What are the three changes that occur inside the airways during an asthma attack?

Solution:

Inflammation and the production of a thick mucus; constriction of the airway muscles, or bronchospasm; and an increased sensitivity to allergens.

Review Questions

Exercise:

Problem:

Which of the following anatomical structures is *not* part of the conducting zone?

- a. pharynx
- b. nasal cavity
- c. alveoli
- d. bronchi

Solution:

C

Exercise:

Problem: What is the function of the conchae in the nasal cavity?

- a. increase surface area
- b. exchange gases
- c. maintain surface tension
- d. maintain air pressure

Solution:

A

Exercise:

Problem:

The fauces connects which of the following structures to the oropharynx?

- a. nasopharynx
- b. laryngopharynx

- c. nasal cavity
 - d. oral cavity
-

Solution:

D

Exercise:

Problem: Which of the following are structural features of the trachea?

- a. C-shaped cartilage
 - b. smooth muscle fibers
 - c. cilia
 - d. all of the above
-

Solution:

A

Exercise:

Problem:

Which of the following structures is *not* part of the bronchial tree?

- a. alveoli
 - b. bronchi
 - c. terminal bronchioles
 - d. respiratory bronchioles
-

Solution:

C

Exercise:

Problem:What is the role of alveolar macrophages?

- a. to secrete pulmonary surfactant
- b. to secrete antimicrobial proteins
- c. to remove pathogens and debris
- d. to facilitate gas exchange

Solution:

C

Critical Thinking Questions

Exercise:

Problem:Describe the three regions of the pharynx and their functions.

Solution:

The pharynx has three major regions. The first region is the nasopharynx, which is connected to the posterior nasal cavity and functions as an airway. The second region is the oropharynx, which is continuous with the nasopharynx and is connected to the oral cavity at the fauces. The laryngopharynx is connected to the oropharynx and the esophagus and trachea. Both the oropharynx and laryngopharynx are passageways for air and food and drink.

Exercise:

Problem:

If a person sustains an injury to the epiglottis, what would be the physiological result?

Solution:

The epiglottis is a region of the larynx that is important during the swallowing of food or drink. As a person swallows, the pharynx moves upward and the epiglottis closes over the trachea, preventing food or drink from entering the trachea. If a person's epiglottis were injured, this mechanism would be impaired. As a result, the person may have problems with food or drink entering the trachea, and possibly, the lungs. Over time, this may cause infections such as pneumonia to set in.

Exercise:

Problem: Compare and contrast the conducting and respiratory zones.

Solution:

The conducting zone of the respiratory system includes the organs and structures that are not directly involved in gas exchange, but perform other duties such as providing a passageway for air, trapping and removing debris and pathogens, and warming and humidifying incoming air. Such structures include the nasal cavity, pharynx, larynx, trachea, and most of the bronchial tree. The respiratory zone includes all the organs and structures that are directly involved in gas exchange, including the respiratory bronchioles, alveolar ducts, and alveoli.

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Glossary

ala

(plural = alae) small, flaring structure of a nostril that forms the lateral side of the nares

alar cartilage

cartilage that supports the apex of the nose and helps shape the nares; it is connected to the septal cartilage and connective tissue of the alae

alveolar duct

small tube that leads from the terminal bronchiole to the respiratory bronchiole and is the point of attachment for alveoli

alveolar macrophage

immune system cell of the alveolus that removes debris and pathogens

alveolar pore

opening that allows airflow between neighboring alveoli

alveolar sac

cluster of alveoli

alveolus

small, grape-like sac that performs gas exchange in the lungs

apex

tip of the external nose

bronchial tree

collective name for the multiple branches of the bronchi and bronchioles of the respiratory system

bridge

portion of the external nose that lies in the area of the nasal bones

bronchiole

branch of bronchi that are 1 mm or less in diameter and terminate at alveolar sacs

bronchus

tube connected to the trachea that branches into many subsidiaries and provides a passageway for air to enter and leave the lungs

conducting zone

region of the respiratory system that includes the organs and structures that provide passageways for air and are not directly involved in gas exchange

cricoid cartilage

portion of the larynx composed of a ring of cartilage with a wide posterior region and a thinner anterior region; attached to the esophagus

dorsum nasi

intermediate portion of the external nose that connects the bridge to the apex and is supported by the nasal bone

epiglottis

leaf-shaped piece of elastic cartilage that is a portion of the larynx that swings to close the trachea during swallowing

external nose

region of the nose that is easily visible to others

fauces

portion of the posterior oral cavity that connects the oral cavity to the oropharynx

fibroelastic membrane

specialized membrane that connects the ends of the C-shape cartilage in the trachea; contains smooth muscle fibers

glottis

opening between the vocal folds through which air passes when producing speech

laryngeal prominence

region where the two lamina of the thyroid cartilage join, forming a protrusion known as “Adam’s apple”

laryngopharynx

portion of the pharynx bordered by the oropharynx superiorly and esophagus and trachea inferiorly; serves as a route for both air and food

larynx

cartilaginous structure that produces the voice, prevents food and beverages from entering the trachea, and regulates the volume of air that enters and leaves the lungs

lingual tonsil

lymphoid tissue located at the base of the tongue

meatus

one of three recesses (superior, middle, and inferior) in the nasal cavity attached to the conchae that increase the surface area of the nasal cavity

naris

(plural = nares) opening of the nostrils

nasal bone

bone of the skull that lies under the root and bridge of the nose and is connected to the frontal and maxillary bones

nasal septum

wall composed of bone and cartilage that separates the left and right nasal cavities

nasopharynx

portion of the pharynx flanked by the conchae and oropharynx that serves as an airway

oropharynx

portion of the pharynx flanked by the nasopharynx, oral cavity, and laryngopharynx that is a passageway for both air and food

palatine tonsil

one of the paired structures composed of lymphoid tissue located anterior to the uvula at the roof of isthmus of the fauces

paranasal sinus

one of the cavities within the skull that is connected to the conchae that serve to warm and humidify incoming air, produce mucus, and lighten the weight of the skull; consists of frontal, maxillary, sphenoidal, and ethmoidal sinuses

pharyngeal tonsil

structure composed of lymphoid tissue located in the nasopharynx

pharynx

region of the conducting zone that forms a tube of skeletal muscle lined with respiratory epithelium; located between the nasal conchae and the esophagus and trachea

philtrum

concave surface of the face that connects the apex of the nose to the top lip

pulmonary surfactant

substance composed of phospholipids and proteins that reduces the surface tension of the alveoli; made by type II alveolar cells

respiratory bronchiole

specific type of bronchiole that leads to alveolar sacs

respiratory epithelium

ciliated lining of much of the conducting zone that is specialized to remove debris and pathogens, and produce mucus

respiratory membrane

alveolar and capillary wall together, which form an air-blood barrier that facilitates the simple diffusion of gases

respiratory zone

includes structures of the respiratory system that are directly involved in gas exchange

root

region of the external nose between the eyebrows

thyroid cartilage

largest piece of cartilage that makes up the larynx and consists of two lamina

trachea

tube composed of cartilaginous rings and supporting tissue that connects the lung bronchi and the larynx; provides a route for air to enter and exit the lung

trachealis muscle

smooth muscle located in the fibroelastic membrane of the trachea

true vocal cord

one of the pair of folded, white membranes that have a free inner edge that oscillates as air passes through to produce sound

type I alveolar cell

squamous epithelial cells that are the major cell type in the alveolar wall; highly permeable to gases

type II alveolar cell

cuboidal epithelial cells that are the minor cell type in the alveolar wall; secrete pulmonary surfactant

vestibular fold

part of the folded region of the glottis composed of mucous membrane; supports the epiglottis during swallowing

The Lungs

By the end of this section, you will be able to:

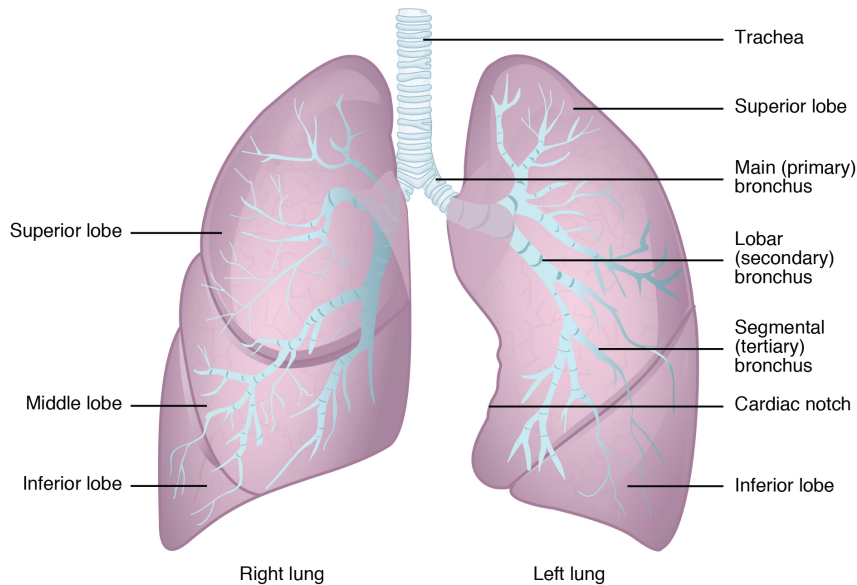
- Describe the overall function of the lung
- Summarize the blood flow pattern associated with the lungs
- Outline the anatomy of the blood supply to the lungs
- Describe the pleura of the lungs and their function

A major organ of the respiratory system, each **lung** houses structures of both the conducting and respiratory zones. The main function of the lungs is to perform the exchange of oxygen and carbon dioxide with air from the atmosphere. To this end, the lungs exchange respiratory gases across a very large epithelial surface area—about 70 square meters—that is highly permeable to gases.

Gross Anatomy of the Lungs

The lungs are pyramid-shaped, paired organs that are connected to the trachea by the right and left bronchi; on the inferior surface, the lungs are bordered by the diaphragm. The diaphragm is the flat, dome-shaped muscle located at the base of the lungs and thoracic cavity. The lungs are enclosed by the pleurae, which are attached to the mediastinum. The right lung is shorter and wider than the left lung, and the left lung occupies a smaller volume than the right. The **cardiac notch** is an indentation on the surface of the left lung, and it allows space for the heart ([\[link\]](#)). The apex of the lung is the superior region, whereas the base is the opposite region near the diaphragm. The costal surface of the lung borders the ribs. The mediastinal surface faces the midline.

Gross Anatomy of the Lungs



Each lung is composed of smaller units called lobes. Fissures separate these lobes from each other. The right lung consists of three lobes: the superior, middle, and inferior lobes. The left lung consists of two lobes: the superior and inferior lobes. A bronchopulmonary segment is a division of a lobe, and each lobe houses multiple bronchopulmonary segments. Each segment receives air from its own tertiary bronchus and is supplied with blood by its own artery. Some diseases of the lungs typically affect one or more bronchopulmonary segments, and in some cases, the diseased segments can be surgically removed with little influence on neighboring segments. A pulmonary lobule is a subdivision formed as the bronchi branch into bronchioles. Each lobule receives its own large bronchiole that has multiple branches. An interlobular septum is a wall, composed of connective tissue, which separates lobules from one another.

Blood Supply and Nervous Innervation of the Lungs

The blood supply of the lungs plays an important role in gas exchange and serves as a transport system for gases throughout the body. In addition, innervation by both the parasympathetic and sympathetic nervous systems provides an important level of control through dilation and constriction of the airway.

Blood Supply

The major function of the lungs is to perform gas exchange, which requires blood from the pulmonary circulation. This blood supply contains deoxygenated blood and travels to the lungs where erythrocytes, also known as red blood cells, pick up oxygen to be transported to tissues throughout the body. The **pulmonary artery** is an artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli. The pulmonary artery branches multiple times as it follows the bronchi, and each branch becomes progressively smaller in diameter. One arteriole and an accompanying venule supply and drain one pulmonary lobule. As they near the alveoli, the pulmonary arteries become the pulmonary capillary network. The pulmonary capillary network consists of tiny vessels with very thin walls that lack smooth muscle fibers. The capillaries branch and follow the bronchioles and structure of the alveoli. It is at this point that the capillary wall meets the alveolar wall, creating the respiratory membrane. Once the blood is oxygenated, it drains from the alveoli by way of multiple pulmonary veins, which exit the lungs through the **hilum**.

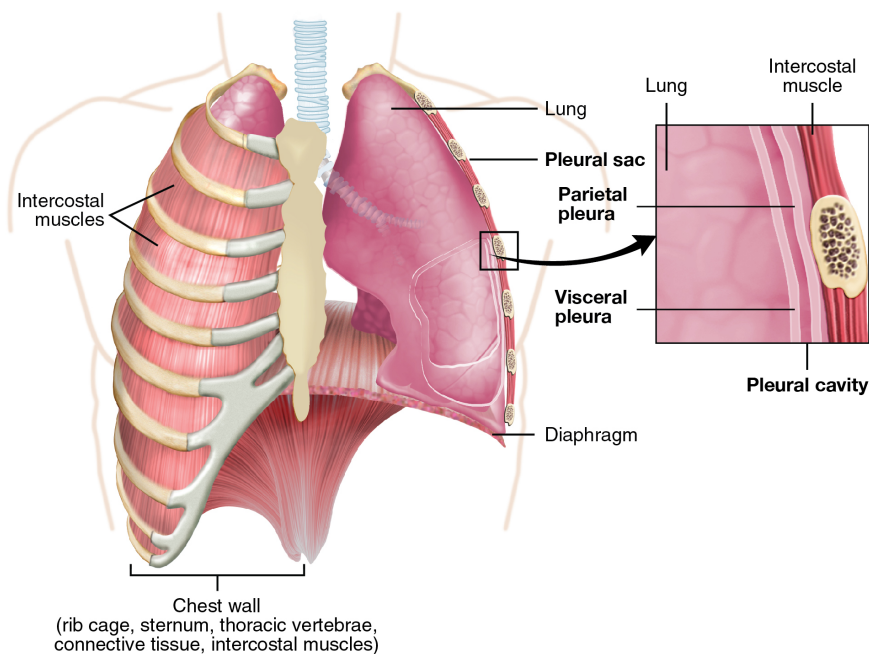
Nervous Innervation

Dilation and constriction of the airway are achieved through nervous control by the parasympathetic and sympathetic nervous systems. The parasympathetic system causes **bronchoconstriction**, whereas the sympathetic nervous system stimulates **bronchodilation**. Reflexes such as coughing, and the ability of the lungs to regulate oxygen and carbon dioxide levels, also result from this autonomic nervous system control. Sensory nerve fibers arise from the vagus nerve, and from the second to fifth thoracic ganglia. The **pulmonary plexus** is a region on the lung root formed by the entrance of the nerves at the hilum. The nerves then follow the bronchi in the lungs and branch to innervate muscle fibers, glands, and blood vessels.

Pleura of the Lungs

Each lung is enclosed within a cavity that is surrounded by the pleura. The pleura (plural = pleurae) is a serous membrane that surrounds the lung. The right and left pleurae, which enclose the right and left lungs, respectively, are separated by the mediastinum. The pleurae consist of two layers. The **visceral pleura** is the layer that is superficial to the lungs, and extends into and lines the lung fissures ([\[link\]](#)). In contrast, the **parietal pleura** is the outer layer that connects to the thoracic wall, the mediastinum, and the diaphragm. The visceral and parietal pleurae connect to each other at the hilum. The **pleural cavity** is the space between the visceral and parietal layers.

Parietal and Visceral Pleurae of the Lungs



The pleurae perform two major functions: They produce pleural fluid and create cavities that separate the major organs. **Pleural fluid** is secreted by mesothelial cells from both pleural layers and acts to lubricate their surfaces. This lubrication reduces friction between the two layers to prevent trauma during breathing, and creates surface tension that helps maintain the position of the lungs against the thoracic wall. This adhesive characteristic of the pleural fluid causes the lungs to enlarge when the thoracic wall expands during ventilation, allowing the lungs to fill with air. The pleurae also create a division between major organs that prevents interference due to the movement of the organs, while preventing the spread of infection.

Note:**Everyday Connection****The Effects of Second-Hand Tobacco Smoke**

The burning of a tobacco cigarette creates multiple chemical compounds that are released through mainstream smoke, which is inhaled by the smoker, and through sidestream smoke, which is the smoke that is given off by the burning cigarette. Second-hand smoke, which is a combination of sidestream smoke and the mainstream smoke that is exhaled by the smoker, has been demonstrated by numerous scientific studies to cause disease. At least 40 chemicals in sidestream smoke have been identified that negatively impact human health, leading to the development of cancer or other conditions, such as immune system dysfunction, liver toxicity, cardiac arrhythmias, pulmonary edema, and neurological dysfunction. Furthermore, second-hand smoke has been found to harbor at least 250 compounds that are known to be toxic, carcinogenic, or both. Some major classes of carcinogens in second-hand smoke are polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines, aromatic amines, formaldehyde, and acetaldehyde.

Tobacco and second-hand smoke are considered to be carcinogenic. Exposure to second-hand smoke can cause lung cancer in individuals who are not tobacco users themselves. It is estimated that the risk of developing lung cancer is increased by up to 30 percent in nonsmokers who live with an individual who smokes in the house, as compared to nonsmokers who are not regularly exposed to second-hand smoke. Children are especially affected by second-hand smoke. Children who live with an individual who smokes inside the home have a larger number of lower respiratory infections, which are associated with hospitalizations, and higher risk of sudden infant death syndrome (SIDS). Second-hand smoke in the home has also been linked to a greater number of ear infections in children, as well as worsening symptoms of asthma.

Chapter Review

The lungs are the major organs of the respiratory system and are responsible for performing gas exchange. The lungs are paired and separated into lobes;

The left lung consists of two lobes, whereas the right lung consists of three lobes. Blood circulation is very important, as blood is required to transport oxygen from the lungs to other tissues throughout the body. The function of the pulmonary circulation is to aid in gas exchange. The pulmonary artery provides deoxygenated blood to the capillaries that form respiratory membranes with the alveoli, and the pulmonary veins return newly oxygenated blood to the heart for further transport throughout the body. The lungs are innervated by the parasympathetic and sympathetic nervous systems, which coordinate the bronchodilation and bronchoconstriction of the airways. The lungs are enclosed by the pleura, a membrane that is composed of visceral and parietal pleural layers. The space between these two layers is called the pleural cavity. The mesothelial cells of the pleural membrane create pleural fluid, which serves as both a lubricant (to reduce friction during breathing) and as an adhesive to adhere the lungs to the thoracic wall (to facilitate movement of the lungs during ventilation).

Review Questions

Exercise:

Problem:

Which of the following structures separates the lung into lobes?

- a. mediastinum
- b. fissure
- c. root
- d. pleura

Solution:

B

Exercise:

Problem:

A section of the lung that receives its own tertiary bronchus is called the _____.

- a. bronchopulmonary segment
- b. pulmonary lobule
- c. interpulmonary segment
- d. respiratory segment

Solution:

A

Exercise:**Problem:**

The _____ circulation picks up oxygen for cellular use and drops off carbon dioxide for removal from the body.

- a. pulmonary
- b. interlobular
- c. respiratory
- d. bronchial

Solution:

C

Exercise:**Problem:**

The pleura that surrounds the lungs consists of two layers, the _____.

- a. visceral and parietal pleurae.

- b. mediastinum and parietal pleurae.
- c. visceral and mediastinum pleurae.
- d. none of the above

Solution:

A

Critical Thinking Questions

Exercise:

Problem: Compare and contrast the right and left lungs.

Solution:

The right and left lungs differ in size and shape to accommodate other organs that encroach on the thoracic region. The right lung consists of three lobes and is shorter than the left lung, due to the position of the liver underneath it. The left lung consists of two lobes and is longer and narrower than the right lung. The left lung has a concave region on the mediastinal surface called the cardiac notch that allows space for the heart.

Exercise:

Problem: Why are the pleurae not damaged during normal breathing?

Solution:

There is a cavity, called the pleural cavity, between the parietal and visceral layers of the pleura. Mesothelial cells produce and secrete pleural fluid into the pleural cavity that acts as a lubricant. Therefore, as you breathe, the pleural fluid prevents the two layers of the pleura from rubbing against each other and causing damage due to friction.

Glossary

bronchoconstriction

decrease in the size of the bronchiole due to contraction of the muscular wall

bronchodilation

increase in the size of the bronchiole due to contraction of the muscular wall

cardiac notch

indentation on the surface of the left lung that allows space for the heart

hilum

concave structure on the mediastinal surface of the lungs where blood vessels, lymphatic vessels, nerves, and a bronchus enter the lung

lung

organ of the respiratory system that performs gas exchange

parietal pleura

outermost layer of the pleura that connects to the thoracic wall, mediastinum, and diaphragm

pleural cavity

space between the visceral and parietal pleurae

pleural fluid

substance that acts as a lubricant for the visceral and parietal layers of the pleura during the movement of breathing

pulmonary artery

artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli

pulmonary plexus

network of autonomic nervous system fibers found near the hilum of the lung

visceral pleura

innermost layer of the pleura that is superficial to the lungs and extends into the lung fissures

The Process of Breathing

By the end of this section, you will be able to:

- Describe the mechanisms that drive breathing
- Discuss how pressure, volume, and resistance are related
- List the steps involved in pulmonary ventilation
- Discuss the physical factors related to breathing
- Discuss the meaning of respiratory volume and capacities
- Define respiratory rate
- Outline the mechanisms behind the control of breathing
- Describe the respiratory centers of the medulla oblongata
- Describe the respiratory centers of the pons
- Discuss factors that can influence the respiratory rate

Pulmonary ventilation is the act of breathing, which can be described as the movement of air into and out of the lungs. The major mechanisms that drive pulmonary ventilation are atmospheric pressure (P_{atm}); the air pressure within the alveoli, called intra-alveolar pressure (P_{alv}); and the pressure within the pleural cavity, called intrapleural pressure (P_{ip}).

Mechanisms of Breathing

The intra-alveolar and intrapleural pressures are dependent on certain physical features of the lung. However, the ability to breathe—to have air enter the lungs during inspiration and air leave the lungs during expiration—is dependent on the air pressure of the atmosphere and the air pressure within the lungs.

Pressure Relationships

Inspiration (or inhalation) and expiration (or exhalation) are dependent on the differences in pressure between the atmosphere and the lungs. In a gas, pressure is a force created by the movement of gas molecules that are confined. For example, a certain number of gas molecules in a two-liter container has more room than the same number of gas molecules in a one-liter container ([\[link\]](#)). In this case, the force exerted by the movement of

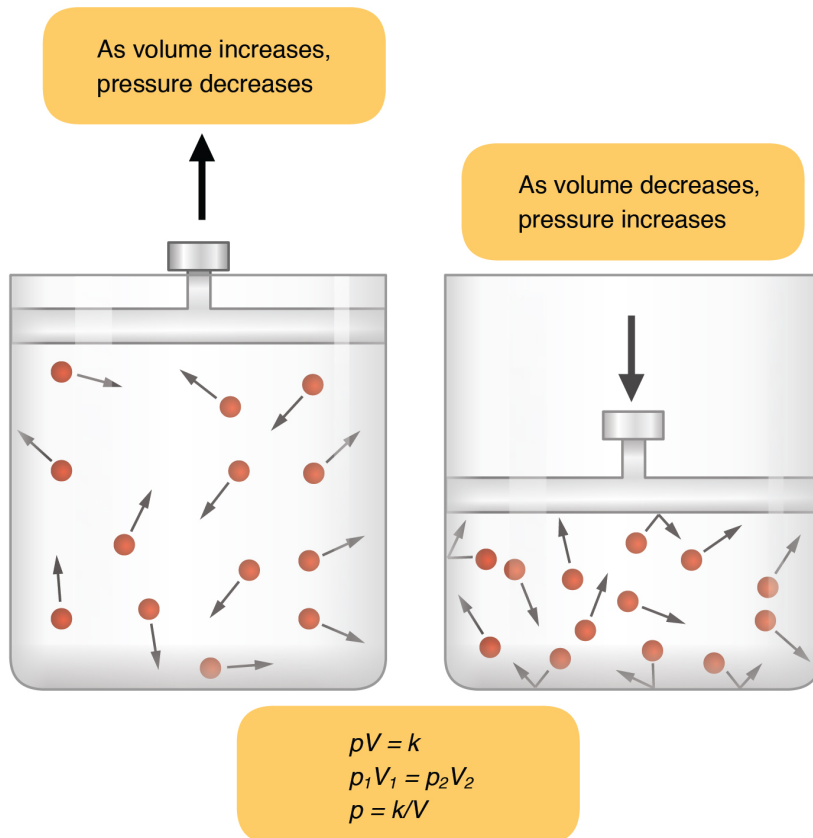
the gas molecules against the walls of the two-liter container is lower than the force exerted by the gas molecules in the one-liter container. Therefore, the pressure is lower in the two-liter container and higher in the one-liter container. At a constant temperature, changing the volume occupied by the gas changes the pressure, as does changing the number of gas molecules. **Boyle's law** describes the relationship between volume and pressure in a gas at a constant temperature. Boyle discovered that the pressure of a gas is inversely proportional to its volume: If volume increases, pressure decreases. Likewise, if volume decreases, pressure increases. Pressure and volume are inversely related ($P = k/V$). Therefore, the pressure in the one-liter container (one-half the volume of the two-liter container) would be twice the pressure in the two-liter container. Boyle's law is expressed by the following formula:

Equation:

$$P_1V_1 = P_2V_2$$

In this formula, P_1 represents the initial pressure and V_1 represents the initial volume, whereas the final pressure and volume are represented by P_2 and V_2 , respectively. If the two- and one-liter containers were connected by a tube and the volume of one of the containers were changed, then the gases would move from higher pressure (lower volume) to lower pressure (higher volume).

Boyle's Law

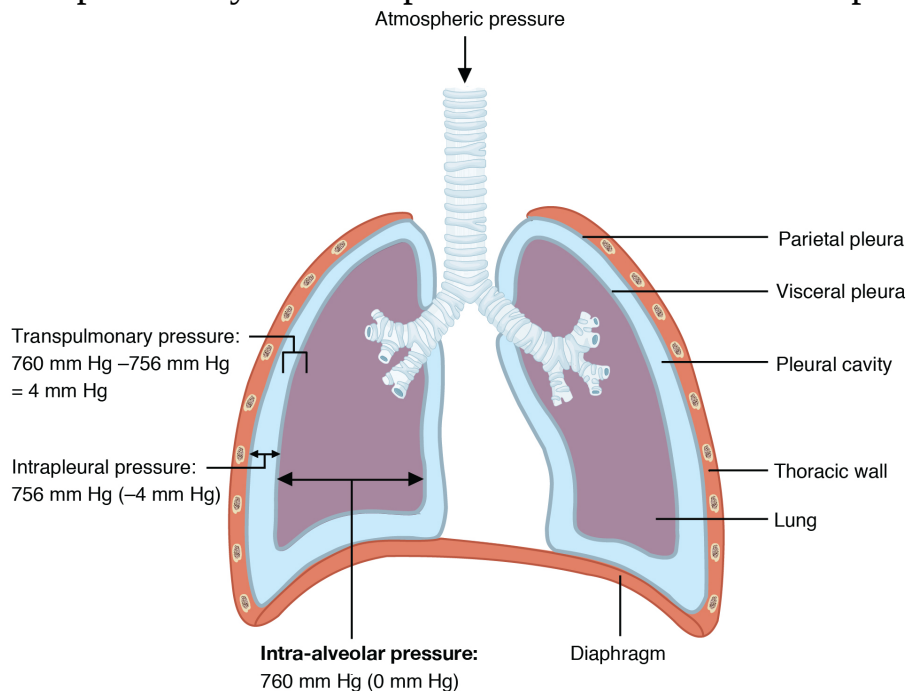


In a gas, pressure increases as volume decreases.

Pulmonary ventilation is dependent on three types of pressure: atmospheric, intra-alveolar, and intrapleural. **Atmospheric pressure** is the amount of force that is exerted by gases in the air surrounding any given surface, such as the body. Atmospheric pressure can be expressed in terms of the unit atmosphere, abbreviated atm, or in millimeters of mercury (mm Hg). One atm is equal to 760 mm Hg, which is the atmospheric pressure at sea level. Typically, for respiration, other pressure values are discussed in relation to atmospheric pressure. Therefore, negative pressure is pressure lower than the atmospheric pressure, whereas positive pressure is pressure that it is greater than the atmospheric pressure. A pressure that is equal to the atmospheric pressure is expressed as zero.

Intra-alveolar pressure (intrapulmonary pressure) is the pressure of the air within the alveoli, which changes during the different phases of breathing ([link](#)). Because the alveoli are connected to the atmosphere via the tubing of the airways (similar to the two- and one-liter containers in the example above), the intrapulmonary pressure of the alveoli always equalizes with the atmospheric pressure.

Intrapulmonary and Intrapleural Pressure Relationships



Intra-alveolar pressure changes during the different phases of the cycle. It equalizes at 760 mm Hg but does not remain at 760 mm Hg.

Intrapleural pressure is the pressure of the air within the pleural cavity, between the visceral and parietal pleurae. Similar to intra-alveolar pressure, intrapleural pressure also changes during the different phases of breathing. However, due to certain characteristics of the lungs, the intrapleural pressure is always lower than, or negative to, the intra-alveolar pressure (and therefore also to atmospheric pressure). Although it fluctuates during inspiration and expiration, intrapleural pressure remains approximately -4 mm Hg throughout the breathing cycle.

Competing forces within the thorax cause the formation of the negative intrapleural pressure. One of these forces relates to the elasticity of the lungs themselves—elastic tissue pulls the lungs inward, away from the thoracic wall. Surface tension of alveolar fluid, which is mostly water, also creates an inward pull of the lung tissue. This inward tension from the lungs is countered by opposing forces from the pleural fluid and thoracic wall. Surface tension within the pleural cavity pulls the lungs outward. Too much or too little pleural fluid would hinder the creation of the negative intrapleural pressure; therefore, the level must be closely monitored by the mesothelial cells and drained by the lymphatic system. Since the parietal pleura is attached to the thoracic wall, the natural elasticity of the chest wall opposes the inward pull of the lungs. Ultimately, the outward pull is slightly greater than the inward pull, creating the -4 mm Hg intrapleural pressure relative to the intra-alveolar pressure. **Transpulmonary pressure** is the difference between the intrapleural and intra-alveolar pressures, and it determines the size of the lungs. A higher transpulmonary pressure corresponds to a larger lung.

Physical Factors Affecting Ventilation

In addition to the differences in pressures, breathing is also dependent upon the contraction and relaxation of muscle fibers of both the diaphragm and thorax. The lungs themselves are passive during breathing, meaning they are not involved in creating the movement that helps inspiration and expiration. This is because of the adhesive nature of the pleural fluid, which allows the lungs to be pulled outward when the thoracic wall moves during inspiration. The recoil of the thoracic wall during expiration causes compression of the lungs. Contraction and relaxation of the diaphragm and intercostals muscles (found between the ribs) cause most of the pressure changes that result in inspiration and expiration. These muscle movements and subsequent pressure changes cause air to either rush in or be forced out of the lungs.

Other characteristics of the lungs influence the effort that must be expended to ventilate. Resistance is a force that slows motion, in this case, the flow of gases. The size of the airway is the primary factor affecting resistance. A

small tubular diameter forces air through a smaller space, causing more collisions of air molecules with the walls of the airways. The following formula helps to describe the relationship between airway resistance and pressure changes:

Equation:

$$F = \Delta P / R$$

As noted earlier, there is surface tension within the alveoli caused by water present in the lining of the alveoli. This surface tension tends to inhibit expansion of the alveoli. However, pulmonary surfactant secreted by type II alveolar cells mixes with that water and helps reduce this surface tension. Without pulmonary surfactant, the alveoli would collapse during expiration.

Thoracic wall compliance is the ability of the thoracic wall to stretch while under pressure. This can also affect the effort expended in the process of breathing. In order for inspiration to occur, the thoracic cavity must expand. The expansion of the thoracic cavity directly influences the capacity of the lungs to expand. If the tissues of the thoracic wall are not very compliant, it will be difficult to expand the thorax to increase the size of the lungs.

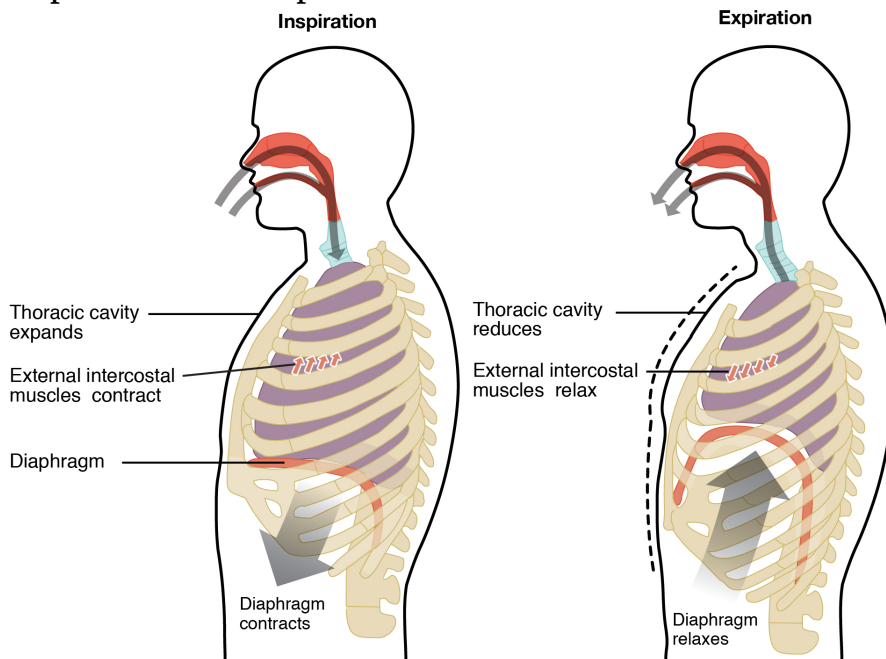
Pulmonary Ventilation

The difference in pressures drives pulmonary ventilation because air flows down a pressure gradient, that is, air flows from an area of higher pressure to an area of lower pressure. Air flows into the lungs largely due to a difference in pressure; atmospheric pressure is greater than intra-alveolar pressure, and intra-alveolar pressure is greater than intrapleural pressure. Air flows out of the lungs during expiration based on the same principle; pressure within the lungs becomes greater than the atmospheric pressure.

Pulmonary ventilation comprises two major steps: inspiration and expiration. **Inspiration** is the process that causes air to enter the lungs, and **expiration** is the process that causes air to leave the lungs ([link](#)). A **respiratory cycle** is one sequence of inspiration and expiration. In general,

two muscle groups are used during normal inspiration: the diaphragm and the external intercostal muscles. Additional muscles can be used if a bigger breath is required. When the diaphragm contracts, it moves inferiorly toward the abdominal cavity, creating a larger thoracic cavity and more space for the lungs. Contraction of the external intercostal muscles moves the ribs upward and outward, causing the rib cage to expand, which increases the volume of the thoracic cavity. Due to the adhesive force of the pleural fluid, the expansion of the thoracic cavity forces the lungs to stretch and expand as well. This increase in volume leads to a decrease in intra-alveolar pressure, creating a pressure lower than atmospheric pressure. As a result, a pressure gradient is created that drives air into the lungs.

Inspiration and Expiration



Inspiration and expiration occur due to the expansion and contraction of the thoracic cavity, respectively.

The process of normal expiration is passive, meaning that energy is not required to push air out of the lungs. Instead, the elasticity of the lung tissue causes the lung to recoil, as the diaphragm and intercostal muscles relax following inspiration. In turn, the thoracic cavity and lungs decrease in

volume, causing an increase in intrapulmonary pressure. The intrapulmonary pressure rises above atmospheric pressure, creating a pressure gradient that causes air to leave the lungs.

There are different types, or modes, of breathing that require a slightly different process to allow inspiration and expiration. **Quiet breathing**, also known as eupnea, is a mode of breathing that occurs at rest and does not require the cognitive thought of the individual. During quiet breathing, the diaphragm and external intercostals must contract.

A deep breath, called diaphragmatic breathing, requires the diaphragm to contract. As the diaphragm relaxes, air passively leaves the lungs. A shallow breath, called costal breathing, requires contraction of the intercostal muscles. As the intercostal muscles relax, air passively leaves the lungs.

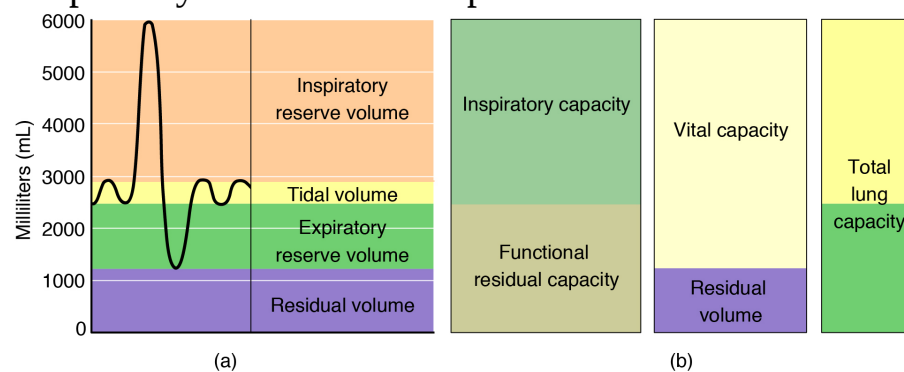
In contrast, **forced breathing**, also known as hyperpnea, is a mode of breathing that can occur during exercise or actions that require the active manipulation of breathing, such as singing. During forced breathing, inspiration and expiration both occur due to muscle contractions. In addition to the contraction of the diaphragm and intercostal muscles, other accessory muscles must also contract. During forced inspiration, muscles of the neck, including the scalenes, contract and lift the thoracic wall, increasing lung volume. During forced expiration, accessory muscles of the abdomen, including the obliques, contract, forcing abdominal organs upward against the diaphragm. This helps to push the diaphragm further into the thorax, pushing more air out. In addition, accessory muscles (primarily the internal intercostals) help to compress the rib cage, which also reduces the volume of the thoracic cavity.

Respiratory Volumes and Capacities

Respiratory volume is the term used for various volumes of air moved by or associated with the lungs at a given point in the respiratory cycle. There are four major types of respiratory volumes: tidal, residual, inspiratory reserve, and expiratory reserve ([\[link\]](#)). **Tidal volume (TV)** is the amount of air that normally enters the lungs during quiet breathing, which is about

500 milliliters. **Expiratory reserve volume (ERV)** is the amount of air you can forcefully exhale past a normal tidal expiration, up to 1200 milliliters for men. **Inspiratory reserve volume (IRV)** is produced by a deep inhalation, past a tidal inspiration. This is the extra volume that can be brought into the lungs during a forced inspiration. **Residual volume (RV)** is the air left in the lungs if you exhale as much air as possible. The residual volume makes breathing easier by preventing the alveoli from collapsing. Respiratory volume is dependent on a variety of factors, and measuring the different types of respiratory volumes can provide important clues about a person's respiratory health ([link](#)).

Respiratory Volumes and Capacities



These two graphs show (a) respiratory volumes and (b) the combination of volumes that results in respiratory capacity.

Pulmonary Function Testing

| Pulmonary function test | Instrument | Measures | Function |
|-------------------------|--------------------|---------------------------------------|---|
| Spirometry | Spirometer | Forced vital capacity (FVC) | Volume of air that is exhaled after maximum inhalation |
| | | Forced expiratory volume (FEV) | Volume of air exhaled during one forced breath |
| | | Forced expiratory flow, 25–75 percent | Air flow in the middle of exhalation |
| | | Peak expiratory flow (PEF) | Rate of exhalation |
| | | Maximum voluntary ventilation (MVV) | Volume of air that can be inspired and expired in 1 minute |
| | | Slow vital capacity (SVC) | Volume of air that can be slowly exhaled after inhaling past the tidal volume |
| | | Total lung capacity (TLC) | Volume of air in the lungs after maximum inhalation |
| | | Functional residual capacity (FRC) | Volume of air left in the lungs after normal expiration |
| | | Residual volume (RV) | Volume of air in the lungs after maximum exhalation |
| | | Total lung capacity (TLC) | Maximum volume of air that the lungs can hold |
| | | Expiratory reserve volume (ERV) | The volume of air that can be exhaled beyond normal exhalation |
| Gas diffusion | Blood gas analyzer | Arterial blood gases | Concentration of oxygen and carbon dioxide in the blood |

Respiratory capacity is the combination of two or more selected volumes, which further describes the amount of air in the lungs during a given time. For example, **total lung capacity (TLC)** is the sum of all of the lung volumes (TV, ERV, IRV, and RV), which represents the total amount of air a person can hold in the lungs after a forceful inhalation. TLC is about 6000 mL air for men, and about 4200 mL for women. **Vital capacity (VC)** is the amount of air a person can move into or out of his or her lungs, and is the sum of all of the volumes except residual volume (TV, ERV, and IRV), which is between 4000 and 5000 milliliters. **Inspiratory capacity (IC)** is the maximum amount of air that can be inhaled past a normal tidal expiration, is the sum of the tidal volume and inspiratory reserve volume. On the other hand, the **functional residual capacity (FRC)** is the amount of air that remains in the lung after a normal tidal expiration; it is the sum of expiratory reserve volume and residual volume (see [\[link\]](#)).

Note:



Watch this [video](#) to learn more about lung volumes and spirometers. Explain how spirometry test results can be used to diagnose respiratory diseases or determine the effectiveness of disease treatment.

In addition to the air that creates respiratory volumes, the respiratory system also contains **anatomical dead space**, which is air that is present in the airway that never reaches the alveoli and therefore never participates in gas exchange. **Alveolar dead space** involves air found within alveoli that are unable to function, such as those affected by disease or abnormal blood flow. **Total dead space** is the anatomical dead space and alveolar dead space together, and represents all of the air in the respiratory system that is not being used in the gas exchange process.

Respiratory Rate and Control of Ventilation

Breathing usually occurs without thought, although at times you can consciously control it, such as when you swim under water, sing a song, or blow bubbles. The **respiratory rate** is the total number of breaths, or respiratory cycles, that occur each minute. Respiratory rate can be an important indicator of disease, as the rate may increase or decrease during an illness or in a disease condition. The respiratory rate is controlled by the respiratory center located within the medulla oblongata in the brain, which responds primarily to changes in carbon dioxide, oxygen, and pH levels in the blood.

The normal respiratory rate of a child decreases from birth to adolescence. A child under 1 year of age has a normal respiratory rate between 30 and 60 breaths per minute, but by the time a child is about 10 years old, the normal

rate is closer to 18 to 30. By adolescence, the normal respiratory rate is similar to that of adults, 12 to 18 breaths per minute.

Ventilation Control Centers

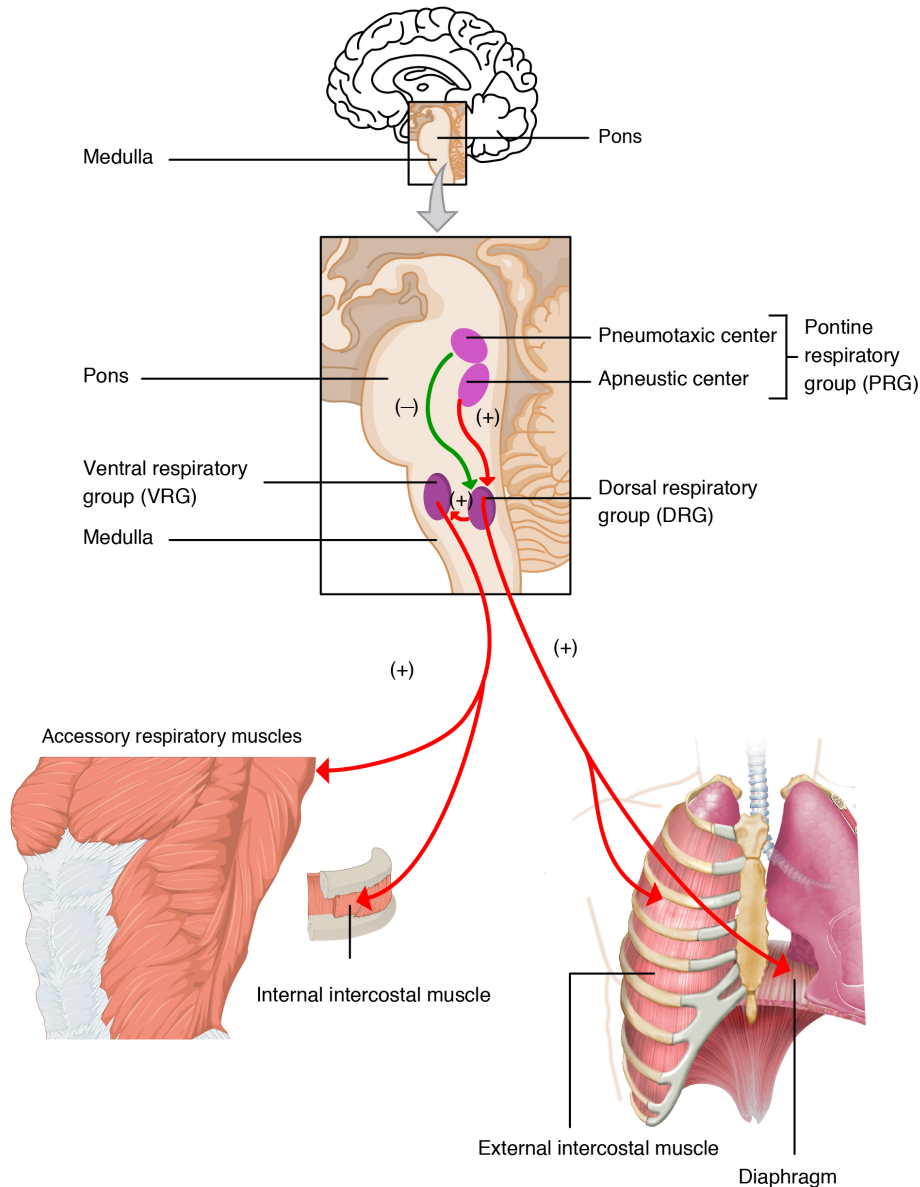
The control of ventilation is a complex interplay of multiple regions in the brain that signal the muscles used in pulmonary ventilation to contract ([link](#)). The result is typically a rhythmic, consistent ventilation rate that provides the body with sufficient amounts of oxygen, while adequately removing carbon dioxide.

| Summary of Ventilation Regulation | |
|-----------------------------------|---|
| System component | Function |
| Medullary respiratory center | Sets the basic rhythm of breathing |
| Ventral respiratory group (VRG) | Generates the breathing rhythm and integrates data coming into the medulla |
| Dorsal respiratory group (DRG) | Integrates input from the stretch receptors and the chemoreceptors in the periphery |
| Pontine respiratory group (PRG) | Influences and modifies the medulla oblongata's functions |

| Summary of Ventilation Regulation | |
|-----------------------------------|---|
| System component | Function |
| Aortic body | Monitors blood PCO ₂ , PO ₂ , and pH |
| Carotid body | Monitors blood PCO ₂ , PO ₂ , and pH |
| Hypothalamus | Monitors emotional state and body temperature |
| Cortical areas of the brain | Control voluntary breathing |
| Proprioceptors | Send impulses regarding joint and muscle movements |
| Pulmonary irritant reflexes | Protect the respiratory zones of the system from foreign material |
| Inflation reflex | Protects the lungs from over-inflating |

Neurons that innervate the muscles of the respiratory system are responsible for controlling and regulating pulmonary ventilation. The major brain centers involved in pulmonary ventilation are the medulla oblongata and the pontine respiratory group ([link](#)).

Respiratory Centers of the Brain



The medulla oblongata contains the **dorsal respiratory group (DRG)** and the **ventral respiratory group (VRG)**. The DRG is involved in maintaining a constant breathing rhythm by stimulating the diaphragm and intercostal muscles to contract, resulting in inspiration. When activity in the DRG ceases, it no longer stimulates the diaphragm and intercostals to contract, allowing them to relax, resulting in expiration. The VRG is involved in forced breathing, as the neurons in the VRG stimulate the accessory muscles involved in forced breathing to contract, resulting in forced inspiration. The VRG also stimulates the accessory muscles involved in forced expiration to contract.

The second respiratory center of the brain is located within the pons, called the pontine respiratory group, and consists of the apneustic and pneumotaxic centers. The **apneustic center** is a double cluster of neuronal cell bodies that stimulate neurons in the DRG, controlling the depth of inspiration, particularly for deep breathing. The **pneumotaxic center** is a network of neurons that inhibits the activity of neurons in the DRG, allowing relaxation after inspiration, and thus controlling the overall rate.

Factors That Affect the Rate and Depth of Respiration

The respiratory rate and the depth of inspiration are regulated by the medulla oblongata and pons; however, these regions of the brain do so in response to systemic stimuli. It is a dose-response, negative-feedback relationship in which the greater the stimulus, the greater the response. Thus, increasing stimuli results in forced breathing. Multiple systemic factors are involved in stimulating the brain to produce pulmonary ventilation.

The major factor that stimulates the medulla oblongata and pons to produce respiration is surprisingly not oxygen concentration, but rather the concentration of carbon dioxide in the blood. As you recall, carbon dioxide is a waste product of cellular respiration and can be toxic. Concentrations of chemicals are sensed by chemoreceptors. A **central chemoreceptor** is one of the specialized receptors that are located in the brain and brainstem, whereas a **peripheral chemoreceptor** is one of the specialized receptors located in the carotid arteries and aortic arch. Concentration changes in certain substances, such as carbon dioxide or hydrogen ions, stimulate these receptors, which in turn signal the respiration centers of the brain. In the case of carbon dioxide, as the concentration of CO_2 in the blood increases, it readily diffuses across the blood-brain barrier, where it collects in the extracellular fluid. As will be explained in more detail later, increased carbon dioxide levels lead to increased levels of hydrogen ions, decreasing pH. The increase in hydrogen ions in the brain triggers the central chemoreceptors to stimulate the respiratory centers to initiate contraction of the diaphragm and intercostal muscles. As a result, the rate and depth of respiration increase, allowing more carbon dioxide to be expelled, which

brings more air into and out of the lungs promoting a reduction in the blood levels of carbon dioxide, and therefore hydrogen ions, in the blood. In contrast, low levels of carbon dioxide in the blood cause low levels of hydrogen ions in the brain, leading to a decrease in the rate and depth of pulmonary ventilation, producing shallow, slow breathing.

Another factor involved in influencing the respiratory activity of the brain is systemic arterial concentrations of hydrogen ions. Increasing carbon dioxide levels can lead to increased H^+ levels, as mentioned above, as well as other metabolic activities, such as lactic acid accumulation after strenuous exercise. Peripheral chemoreceptors of the aortic arch and carotid arteries sense arterial levels of hydrogen ions. When peripheral chemoreceptors sense decreasing, or more acidic, pH levels, they stimulate an increase in ventilation to remove carbon dioxide from the blood at a quicker rate. Removal of carbon dioxide from the blood helps to reduce hydrogen ions, thus increasing systemic pH.

Blood levels of oxygen are also important in influencing respiratory rate. The peripheral chemoreceptors are responsible for sensing large changes in blood oxygen levels. If blood oxygen levels become quite low—about 60 mm Hg or less—then peripheral chemoreceptors stimulate an increase in respiratory activity. The chemoreceptors are only able to sense dissolved oxygen molecules, not the oxygen that is bound to hemoglobin. As you recall, the majority of oxygen is bound by hemoglobin; when dissolved levels of oxygen drop, hemoglobin releases oxygen. Therefore, a large drop in oxygen levels is required to stimulate the chemoreceptors of the aortic arch and carotid arteries.

The hypothalamus and other brain regions associated with the limbic system also play roles in influencing the regulation of breathing by interacting with the respiratory centers. The hypothalamus and other regions associated with the limbic system are involved in regulating respiration in response to emotions, pain, and temperature. For example, an increase in body temperature causes an increase in respiratory rate. Feeling excited or the fight-or-flight response will also result in an increase in respiratory rate.

Note:

Disorders of the...

Respiratory System: Sleep Apnea

Sleep apnea is a chronic disorder that can occur in children or adults, and is characterized by the cessation of breathing during sleep. These episodes may last for several seconds or several minutes, and may differ in the frequency with which they are experienced. Sleep apnea leads to poor sleep, which is reflected in the symptoms of fatigue, evening napping, irritability, memory problems, and morning headaches. In addition, many individuals with sleep apnea experience a dry throat in the morning after waking from sleep, which may be due to excessive snoring.

There are two types of sleep apnea: obstructive sleep apnea and central sleep apnea. Obstructive sleep apnea is caused by an obstruction of the airway during sleep, which can occur at different points in the airway, depending on the underlying cause of the obstruction. For example, the tongue and throat muscles of some individuals with obstructive sleep apnea may relax excessively, causing the muscles to push into the airway.

Another example is obesity, which is a known risk factor for sleep apnea, as excess adipose tissue in the neck region can push the soft tissues towards the lumen of the airway, causing the trachea to narrow.

In central sleep apnea, the respiratory centers of the brain do not respond properly to rising carbon dioxide levels and therefore do not stimulate the contraction of the diaphragm and intercostal muscles regularly. As a result, inspiration does not occur and breathing stops for a short period. In some cases, the cause of central sleep apnea is unknown. However, some medical conditions, such as stroke and congestive heart failure, may cause damage to the pons or medulla oblongata. In addition, some pharmacologic agents, such as morphine, can affect the respiratory centers, causing a decrease in the respiratory rate. The symptoms of central sleep apnea are similar to those of obstructive sleep apnea.

A diagnosis of sleep apnea is usually done during a sleep study, where the patient is monitored in a sleep laboratory for several nights. The patient's blood oxygen levels, heart rate, respiratory rate, and blood pressure are monitored, as are brain activity and the volume of air that is inhaled and exhaled. Treatment of sleep apnea commonly includes the use of a device called a continuous positive airway pressure (CPAP) machine during sleep. The CPAP machine has a mask that covers the nose, or the nose and

mouth, and forces air into the airway at regular intervals. This pressurized air can help to gently force the airway to remain open, allowing more normal ventilation to occur. Other treatments include lifestyle changes to decrease weight, eliminate alcohol and other sleep apnea-promoting drugs, and changes in sleep position. In addition to these treatments, patients with central sleep apnea may need supplemental oxygen during sleep.

Chapter Review

Pulmonary ventilation is the process of breathing, which is driven by pressure differences between the lungs and the atmosphere. Atmospheric pressure is the force exerted by gases present in the atmosphere. The force exerted by gases within the alveoli is called intra-alveolar (intrapulmonary) pressure, whereas the force exerted by gases in the pleural cavity is called intrapleural pressure. Typically, intrapleural pressure is lower, or negative to, intra-alveolar pressure. The difference in pressure between intrapleural and intra-alveolar pressures is called transpulmonary pressure. In addition, intra-alveolar pressure will equalize with the atmospheric pressure. Pressure is determined by the volume of the space occupied by a gas and is influenced by resistance. Air flows when a pressure gradient is created, from a space of higher pressure to a space of lower pressure. Boyle's law describes the relationship between volume and pressure. A gas is at lower pressure in a larger volume because the gas molecules have more space to in which to move. The same quantity of gas in a smaller volume results in gas molecules crowding together, producing increased pressure.

Resistance is created by inelastic surfaces, as well as the diameter of the airways. Resistance reduces the flow of gases. The surface tension of the alveoli also influences pressure, as it opposes the expansion of the alveoli. However, pulmonary surfactant helps to reduce the surface tension so that the alveoli do not collapse during expiration. The ability of the lungs to stretch, called lung compliance, also plays a role in gas flow. The more the lungs can stretch, the greater the potential volume of the lungs. The greater the volume of the lungs, the lower the air pressure within the lungs.

Pulmonary ventilation consists of the process of inspiration (or inhalation), where air enters the lungs, and expiration (or exhalation), where air leaves the lungs. During inspiration, the diaphragm and external intercostal muscles contract, causing the rib cage to expand and move outward, and expanding the thoracic cavity and lung volume. This creates a lower pressure within the lung than that of the atmosphere, causing air to be drawn into the lungs. During expiration, the diaphragm and intercostals relax, causing the thorax and lungs to recoil. The air pressure within the lungs increases to above the pressure of the atmosphere, causing air to be forced out of the lungs. However, during forced exhalation, the internal intercostals and abdominal muscles may be involved in forcing air out of the lungs.

Respiratory volume describes the amount of air in a given space within the lungs, or which can be moved by the lung, and is dependent on a variety of factors. Tidal volume refers to the amount of air that enters the lungs during quiet breathing, whereas inspiratory reserve volume is the amount of air that enters the lungs when a person inhales past the tidal volume. Expiratory reserve volume is the extra amount of air that can leave with forceful expiration, following tidal expiration. Residual volume is the amount of air that is left in the lungs after expelling the expiratory reserve volume.

Respiratory capacity is the combination of two or more volumes.

Anatomical dead space refers to the air within the respiratory structures that never participates in gas exchange, because it does not reach functional alveoli. Respiratory rate is the number of breaths taken per minute, which may change during certain diseases or conditions.

Both respiratory rate and depth are controlled by the respiratory centers of the brain, which are stimulated by factors such as chemical and pH changes in the blood. These changes are sensed by central chemoreceptors, which are located in the brain, and peripheral chemoreceptors, which are located in the aortic arch and carotid arteries. A rise in carbon dioxide or a decline in oxygen levels in the blood stimulates an increase in respiratory rate and depth.

Interactive Link Questions

Exercise:**Problem:**

Watch this [video](#) to learn more about lung volumes and spirometers. Explain how spirometry test results can be used to diagnose respiratory diseases or determine the effectiveness of disease treatment.

Solution:

Patients with respiratory ailments (such as asthma, emphysema, COPD, etc.) have issues with airway resistance and/or lung compliance. Both of these factors can interfere with the patient's ability to move air effectively. A spirometry test can determine how much air the patient can move into and out of the lungs. If the air volumes are low, this can indicate that the patient has a respiratory disease or that the treatment regimen may need to be adjusted. If the numbers are normal, the patient does not have a significant respiratory disease or the treatment regimen is working as expected.

Review Questions**Exercise:****Problem:**

Which of the following processes does atmospheric pressure play a role in?

- a. pulmonary ventilation
- b. production of pulmonary surfactant
- c. resistance
- d. surface tension

Solution:

A

Exercise:

Problem: A decrease in volume leads to a(n) _____ pressure.

- a. decrease in
- b. equalization of
- c. increase in
- d. zero

Solution:

C

Exercise:

Problem:

The pressure difference between the intra-alveolar and intrapleural pressures is called _____.

- a. atmospheric pressure
- b. pulmonary pressure
- c. negative pressure
- d. transpulmonary pressure

Solution:

D

Exercise:

Problem: Gas flow decreases as _____ increases.

- a. resistance
- b. pressure
- c. airway diameter
- d. friction

Solution:

A

Exercise:

Problem:

Contraction of the external intercostal muscles causes which of the following to occur?

- a. The diaphragm moves downward.
- b. The rib cage is compressed.
- c. The thoracic cavity volume decreases.
- d. The ribs and sternum move upward.

Solution:

D

Exercise:

Problem: Which of the following prevents the alveoli from collapsing?

- a. residual volume
- b. tidal volume
- c. expiratory reserve volume
- d. inspiratory reserve volume

Solution:

A

Critical Thinking Questions

Exercise:

Problem: Describe what is meant by the term “lung compliance.”

Solution:

Lung compliance refers to the ability of lung tissue to stretch under pressure, which is determined in part by the surface tension of the alveoli and the ability of the connective tissue to stretch. Lung compliance plays a role in determining how much the lungs can change in volume, which in turn helps to determine pressure and air movement.

Exercise:

Problem: Outline the steps involved in quiet breathing.

Solution:

Quiet breathing occurs at rest and without active thought. During quiet breathing, the diaphragm and external intercostal muscles work at different extents, depending on the situation. For inspiration, the diaphragm contracts, causing the diaphragm to flatten and drop towards the abdominal cavity, helping to expand the thoracic cavity. The external intercostal muscles contract as well, causing the rib cage to expand, and the rib cage and sternum to move outward, also expanding the thoracic cavity. Expansion of the thoracic cavity also causes the lungs to expand, due to the adhesiveness of the pleural fluid. As a result, the pressure within the lungs drops below that of the atmosphere, causing air to rush into the lungs. In contrast, expiration is a passive process. As the diaphragm and intercostal muscles relax, the lungs and thoracic tissues recoil, and the volume of the lungs decreases. This causes the pressure within the lungs to increase above that of the atmosphere, causing air to leave the lungs.

Exercise:

Problem: What is respiratory rate and how is it controlled?

Solution:

Respiratory rate is defined as the number of breaths taken per minute. Respiratory rate is controlled by the respiratory center, located in the medulla oblongata. Conscious thought can alter the normal respiratory rate through control by skeletal muscle, although one cannot consciously stop the rate altogether. A typical resting respiratory rate is about 14 breaths per minute.

Glossary

alveolar dead space

air space within alveoli that are unable to participate in gas exchange

anatomical dead space

air space present in the airway that never reaches the alveoli and therefore never participates in gas exchange

apneustic center

network of neurons within the pons that stimulate the neurons in the dorsal respiratory group; controls the depth of inspiration

atmospheric pressure

amount of force that is exerted by gases in the air surrounding any given surface

Boyle's law

relationship between volume and pressure as described by the formula:

$$P_1V_1 = P_2V_2$$

central chemoreceptor

one of the specialized receptors that are located in the brain that sense changes in hydrogen ion, oxygen, or carbon dioxide concentrations in the brain

dorsal respiratory group (DRG)

region of the medulla oblongata that stimulates the contraction of the diaphragm and intercostal muscles to induce inspiration

expiration

(also, exhalation) process that causes the air to leave the lungs

expiratory reserve volume (ERV)

amount of air that can be forcefully exhaled after a normal tidal exhalation

forced breathing

(also, hyperpnea) mode of breathing that occurs during exercise or by active thought that requires muscle contraction for both inspiration and expiration

functional residual capacity (FRC)

sum of ERV and RV, which is the amount of air that remains in the lungs after a tidal expiration

inspiration

(also, inhalation) process that causes air to enter the lungs

inspiratory capacity (IC)

sum of the TV and IRV, which is the amount of air that can maximally be inhaled past a tidal expiration

inspiratory reserve volume (IRV)

amount of air that enters the lungs due to deep inhalation past the tidal volume

intra-alveolar pressure

(intrapulmonary pressure) pressure of the air within the alveoli

intrapleural pressure

pressure of the air within the pleural cavity

peripheral chemoreceptor

one of the specialized receptors located in the aortic arch and carotid arteries that sense changes in pH, carbon dioxide, or oxygen blood levels

pneumotaxic center

network of neurons within the pons that inhibit the activity of the neurons in the dorsal respiratory group; controls rate of breathing

pulmonary ventilation

exchange of gases between the lungs and the atmosphere; breathing

quiet breathing

(also, eupnea) mode of breathing that occurs at rest and does not require the cognitive thought of the individual

residual volume (RV)

amount of air that remains in the lungs after maximum exhalation

respiratory cycle

one sequence of inspiration and expiration

respiratory rate

total number of breaths taken each minute

respiratory volume

varying amounts of air within the lung at a given time

thoracic wall compliance

ability of the thoracic wall to stretch while under pressure

tidal volume (TV)

amount of air that normally enters the lungs during quiet breathing

total dead space

sum of the anatomical dead space and alveolar dead space

total lung capacity (TLC)

total amount of air that can be held in the lungs; sum of TV, ERV, IRV, and RV

transpulmonary pressure

pressure difference between the intrapleural and intra-alveolar pressures

ventral respiratory group (VRG)

region of the medulla oblongata that stimulates the contraction of the accessory muscles involved in respiration to induce forced inspiration and expiration

vital capacity (VC)

sum of TV, ERV, and IRV, which is all the volumes that participate in gas exchange

Gas Exchange

By the end of this section, you will be able to:

- Compare the composition of atmospheric air and alveolar air
- Describe the mechanisms that drive gas exchange
- Discuss the importance of sufficient ventilation and perfusion, and how the body adapts when they are insufficient
- Discuss the process of external respiration
- Describe the process of internal respiration

The purpose of the respiratory system is to perform gas exchange. Pulmonary ventilation provides air to the alveoli for this gas exchange process. At the respiratory membrane, where the alveolar and capillary walls meet, gases move across the membranes, with oxygen entering the bloodstream and carbon dioxide exiting. It is through this mechanism that blood is oxygenated and carbon dioxide, the waste product of cellular respiration, is removed from the body.

Gas Exchange

In order to understand the mechanisms of gas exchange in the lung, it is important to understand the underlying principles of gases and their behavior. In addition to Boyle's law, several other gas laws help to describe the behavior of gases.

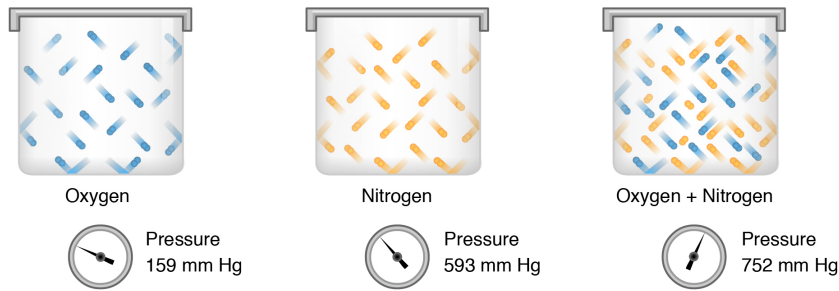
Gas Laws and Air Composition

Gas molecules exert force on the surfaces with which they are in contact; this force is called pressure. In natural systems, gases are normally present as a mixture of different types of molecules. For example, the atmosphere consists of oxygen, nitrogen, carbon dioxide, and other gaseous molecules, and this gaseous mixture exerts a certain pressure referred to as atmospheric pressure ([\[link\]](#)). **Partial pressure** (P_x) is the pressure of a single type of gas in a mixture of gases. For example, in the atmosphere, oxygen exerts a partial pressure, and nitrogen exerts another partial pressure, independent of the partial pressure of oxygen ([\[link\]](#)). **Total pressure** is the sum of all the

partial pressures of a gaseous mixture. **Dalton's law** describes the behavior of nonreactive gases in a gaseous mixture and states that a specific gas type in a mixture exerts its own pressure; thus, the total pressure exerted by a mixture of gases is the sum of the partial pressures of the gases in the mixture.

| Partial Pressures of Atmospheric Gases | | |
|---|-------------------------------------|---------------------------------|
| Gas | Percent of total composition | Partial pressure (mm Hg) |
| Nitrogen (N ₂) | 78.6 | 597.4 |
| Oxygen (O ₂) | 20.9 | 158.8 |
| Water (H ₂ O) | 0.4 | 3.0 |
| Carbon dioxide (CO ₂) | 0.04 | 0.3 |
| Others | 0.06 | 0.5 |
| Total composition/total atmospheric pressure | 100% | 760.0 |

Partial and Total Pressures of a Gas



Partial pressure is the force exerted by a gas.
The sum of the partial pressures of all the gases in a mixture equals the total pressure.

Partial pressure is extremely important in predicting the movement of gases. Recall that gases tend to equalize their pressure in two regions that are connected. A gas will move from an area where its partial pressure is higher to an area where its partial pressure is lower. In addition, the greater the partial pressure difference between the two areas, the more rapid is the movement of gases.

Solubility of Gases in Liquids

Henry's law describes the behavior of gases when they come into contact with a liquid, such as blood. Henry's law states that the concentration of gas in a liquid is directly proportional to the solubility and partial pressure of that gas. The greater the partial pressure of the gas, the greater the number of gas molecules that will dissolve in the liquid. The concentration of the gas in a liquid is also dependent on the solubility of the gas in the liquid. For example, although nitrogen is present in the atmosphere, very little nitrogen dissolves into the blood, because the solubility of nitrogen in blood is very low. The exception to this occurs in scuba divers; the composition of the compressed air that divers breathe causes nitrogen to have a higher partial pressure than normal, causing it to dissolve in the blood in greater amounts than normal. Too much nitrogen in the bloodstream results in a

serious condition that can be fatal if not corrected. Gas molecules establish an equilibrium between those molecules dissolved in liquid and those in air.

The composition of air in the atmosphere and in the alveoli differs. In both cases, the relative concentration of gases is nitrogen > oxygen > water vapor > carbon dioxide. The amount of water vapor present in alveolar air is greater than that in atmospheric air ([link](#)). Recall that the respiratory system works to humidify incoming air, thereby causing the air present in the alveoli to have a greater amount of water vapor than atmospheric air. In addition, alveolar air contains a greater amount of carbon dioxide and less oxygen than atmospheric air. This is no surprise, as gas exchange removes oxygen from and adds carbon dioxide to alveolar air. Both deep and forced breathing cause the alveolar air composition to be changed more rapidly than during quiet breathing. As a result, the partial pressures of oxygen and carbon dioxide change, affecting the diffusion process that moves these materials across the membrane. This will cause oxygen to enter and carbon dioxide to leave the blood more quickly.

| Composition and Partial Pressures of Alveolar Air | | |
|---|------------------------------|--------------------------|
| Gas | Percent of total composition | Partial pressure (mm Hg) |
| Nitrogen (N ₂) | 74.9 | 569 |
| Oxygen (O ₂) | 13.7 | 104 |
| Water (H ₂ O) | 6.2 | 40 |
| Carbon dioxide (CO ₂) | 5.2 | 47 |

| Composition and Partial Pressures of Alveolar Air | | |
|--|-------------------------------------|---------------------------------|
| Gas | Percent of total composition | Partial pressure (mm Hg) |
| Total composition/total alveolar pressure | 100% | 760.0 |

Ventilation and Perfusion

Two important aspects of gas exchange in the lung are ventilation and perfusion. **Ventilation** is the movement of air into and out of the lungs, and perfusion is the flow of blood in the pulmonary capillaries. For gas exchange to be efficient, the volumes involved in ventilation and perfusion should be compatible. However, factors such as regional gravity effects on blood, blocked alveolar ducts, or disease can cause ventilation and perfusion to be imbalanced.

The partial pressure of oxygen in alveolar air is about 104 mm Hg, whereas the partial pressure of oxygenated blood in pulmonary veins is about 100 mm Hg. When ventilation is sufficient, oxygen enters the alveoli at a high rate, and the partial pressure of oxygen in the alveoli remains high. In contrast, when ventilation is insufficient, the partial pressure of oxygen in the alveoli drops. Without the large difference in partial pressure between the alveoli and the blood, oxygen does not diffuse efficiently across the respiratory membrane. The body has mechanisms that counteract this problem. In cases when ventilation is not sufficient for an alveolus, the body redirects blood flow to alveoli that are receiving sufficient ventilation. This is achieved by constricting the pulmonary arterioles that serve the dysfunctional alveolus, which redirects blood to other alveoli that have sufficient ventilation. At the same time, the pulmonary arterioles that serve alveoli receiving sufficient ventilation vasodilate, which brings in greater blood flow. Factors such as carbon dioxide, oxygen, and pH levels can all

serve as stimuli for adjusting blood flow in the capillary networks associated with the alveoli.

Ventilation is regulated by the diameter of the airways, whereas perfusion is regulated by the diameter of the blood vessels. The diameter of the bronchioles is sensitive to the partial pressure of carbon dioxide in the alveoli. A greater partial pressure of carbon dioxide in the alveoli causes the bronchioles to increase their diameter as will a decreased level of oxygen in the blood supply, allowing carbon dioxide to be exhaled from the body at a greater rate. As mentioned above, a greater partial pressure of oxygen in the alveoli causes the pulmonary arterioles to dilate, increasing blood flow.

Gas Exchange

Gas exchange occurs at two sites in the body: in the lungs, where oxygen is picked up and carbon dioxide is released at the respiratory membrane, and at the tissues, where oxygen is released and carbon dioxide is picked up. External respiration is the exchange of gases with the external environment, and occurs in the alveoli of the lungs. Internal respiration is the exchange of gases with the internal environment, and occurs in the tissues. The actual exchange of gases occurs due to simple diffusion. Energy is not required to move oxygen or carbon dioxide across membranes. Instead, these gases follow pressure gradients that allow them to diffuse. The anatomy of the lung maximizes the diffusion of gases: The respiratory membrane is highly permeable to gases; the respiratory and blood capillary membranes are very thin; and there is a large surface area throughout the lungs.

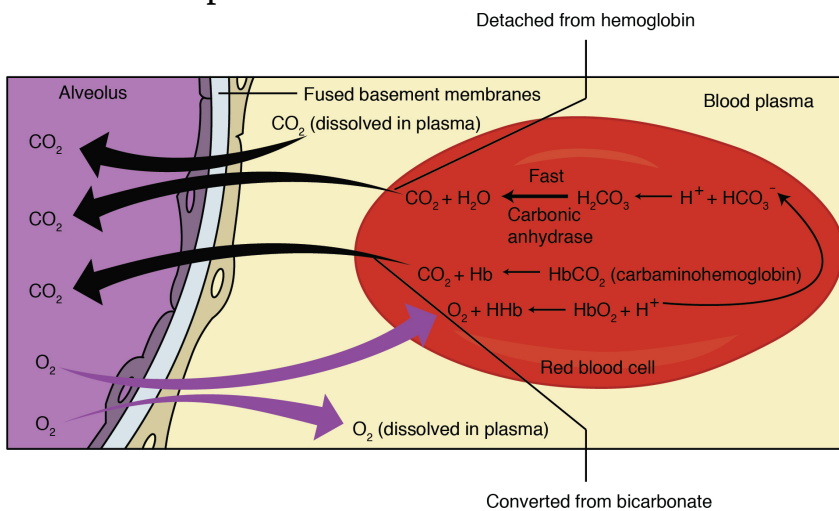
External Respiration

The pulmonary artery carries deoxygenated blood into the lungs from the heart, where it branches and eventually becomes the capillary network composed of pulmonary capillaries. These pulmonary capillaries create the respiratory membrane with the alveoli ([\[link\]](#)). As the blood is pumped through this capillary network, gas exchange occurs. Although a small amount of the oxygen is able to dissolve directly into plasma from the

alveoli, most of the oxygen is picked up by erythrocytes (red blood cells) and binds to a protein called hemoglobin, a process described later in this chapter. Oxygenated hemoglobin is red, causing the overall appearance of bright red oxygenated blood, which returns to the heart through the pulmonary veins. Carbon dioxide is released in the opposite direction of oxygen, from the blood to the alveoli. Some of the carbon dioxide is returned on hemoglobin, but can also be dissolved in plasma or is present as a converted form, also explained in greater detail later in this chapter.

External respiration occurs as a function of partial pressure differences in oxygen and carbon dioxide between the alveoli and the blood in the pulmonary capillaries.

External Respiration



In external respiration, oxygen diffuses across the respiratory membrane from the alveolus to the capillary, whereas carbon dioxide diffuses out of the capillary into the alveolus.

Although the solubility of oxygen in blood is not high, there is a drastic difference in the partial pressure of oxygen in the alveoli versus in the blood of the pulmonary capillaries. This difference is about 64 mm Hg: The partial pressure of oxygen in the alveoli is about 104 mm Hg, whereas its partial pressure in the blood of the capillary is about 40 mm Hg. This large

difference in partial pressure creates a very strong pressure gradient that causes oxygen to rapidly cross the respiratory membrane from the alveoli into the blood.

The partial pressure of carbon dioxide is also different between the alveolar air and the blood of the capillary. However, the partial pressure difference is less than that of oxygen, about 5 mm Hg. The partial pressure of carbon dioxide in the blood of the capillary is about 45 mm Hg, whereas its partial pressure in the alveoli is about 40 mm Hg. However, the solubility of carbon dioxide is much greater than that of oxygen—by a factor of about 20—in both blood and alveolar fluids. As a result, the relative concentrations of oxygen and carbon dioxide that diffuse across the respiratory membrane are similar.

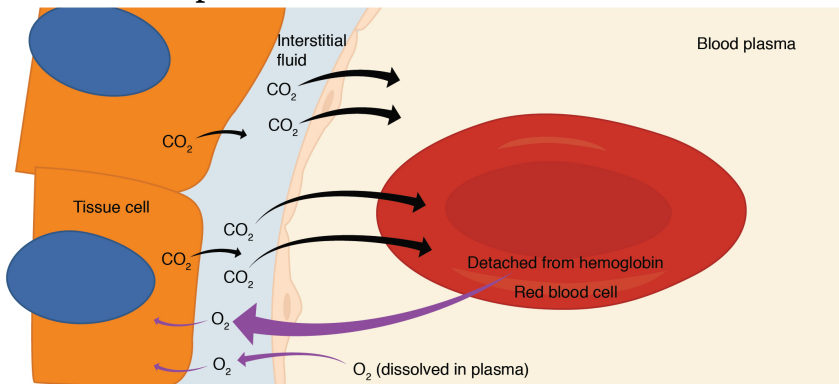
Internal Respiration

Internal respiration is gas exchange that occurs at the level of body tissues ([link](#)). Similar to external respiration, internal respiration also occurs as simple diffusion due to a partial pressure gradient. However, the partial pressure gradients are opposite of those present at the respiratory membrane. The partial pressure of oxygen in tissues is low, about 40 mm Hg, because oxygen is continuously used for cellular respiration. In contrast, the partial pressure of oxygen in the blood is about 100 mm Hg. This creates a pressure gradient that causes oxygen to dissociate from hemoglobin, diffuse out of the blood, cross the interstitial space, and enter the tissue. Hemoglobin that has little oxygen bound to it loses much of its brightness, so that blood returning to the heart is more burgundy in color.

Considering that cellular respiration continuously produces carbon dioxide, the partial pressure of carbon dioxide is lower in the blood than it is in the tissue, causing carbon dioxide to diffuse out of the tissue, cross the interstitial fluid, and enter the blood. It is then carried back to the lungs either bound to hemoglobin, dissolved in plasma, or in a converted form. By the time blood returns to the heart, the partial pressure of oxygen has returned to about 40 mm Hg, and the partial pressure of carbon dioxide has

returned to about 45 mm Hg. The blood is then pumped back to the lungs to be oxygenated once again during external respiration.

Internal Respiration



Oxygen diffuses out of the capillary and into cells, whereas carbon dioxide diffuses out of cells and into the capillary.

Note:

Everyday Connection

Hyperbaric Chamber Treatment

A type of device used in some areas of medicine that exploits the behavior of gases is hyperbaric chamber treatment. A hyperbaric chamber is a unit that can be sealed and expose a patient to either 100 percent oxygen with increased pressure or a mixture of gases that includes a higher concentration of oxygen than normal atmospheric air, also at a higher partial pressure than the atmosphere. There are two major types of chambers: monoplace and multiplace. Monoplace chambers are typically for one patient, and the staff tending to the patient observes the patient from outside of the chamber ([\[link\]](#)). Some facilities have special monoplace hyperbaric chambers that allow multiple patients to be treated at once, usually in a sitting or reclining position, to help ease feelings of isolation or claustrophobia. Multiplace chambers are large enough for multiple patients to be treated at one time, and the staff attending these

patients is present inside the chamber. In a multiplace chamber, patients are often treated with air via a mask or hood, and the chamber is pressurized.

Hyperbaric Chamber



(credit: "komunews"/flickr.com)

Hyperbaric chamber treatment is based on the behavior of gases. As you recall, gases move from a region of higher partial pressure to a region of lower partial pressure. In a hyperbaric chamber, the atmospheric pressure is increased, causing a greater amount of oxygen than normal to diffuse into the bloodstream of the patient. Hyperbaric chamber therapy is used to treat a variety of medical problems, such as wound and graft healing, anaerobic bacterial infections, and carbon monoxide poisoning. Exposure to and poisoning by carbon monoxide is difficult to reverse, because hemoglobin's affinity for carbon monoxide is much stronger than its affinity for oxygen, causing carbon monoxide to replace oxygen in the blood. Hyperbaric chamber therapy can treat carbon monoxide poisoning, because the increased atmospheric pressure causes more oxygen to diffuse into the bloodstream. At this increased pressure and increased concentration of oxygen, carbon monoxide is displaced from hemoglobin. Another example is the treatment of anaerobic bacterial infections, which are created by bacteria that cannot or prefer not to live in the presence of oxygen. An increase in blood and tissue levels of oxygen helps to kill the

anaerobic bacteria that are responsible for the infection, as oxygen is toxic to anaerobic bacteria. For wounds and grafts, the chamber stimulates the healing process by increasing energy production needed for repair. Increasing oxygen transport allows cells to ramp up cellular respiration and thus ATP production, the energy needed to build new structures.

Chapter Review

The behavior of gases can be explained by the principles of Dalton's law and Henry's law, both of which describe aspects of gas exchange. Dalton's law states that each specific gas in a mixture of gases exerts force (its partial pressure) independently of the other gases in the mixture. Henry's law states that the amount of a specific gas that dissolves in a liquid is a function of its partial pressure. The greater the partial pressure of a gas, the more of that gas will dissolve in a liquid, as the gas moves toward equilibrium. Gas molecules move down a pressure gradient; in other words, gas moves from a region of high pressure to a region of low pressure. The partial pressure of oxygen is high in the alveoli and low in the blood of the pulmonary capillaries. As a result, oxygen diffuses across the respiratory membrane from the alveoli into the blood. In contrast, the partial pressure of carbon dioxide is high in the pulmonary capillaries and low in the alveoli. Therefore, carbon dioxide diffuses across the respiratory membrane from the blood into the alveoli. The amount of oxygen and carbon dioxide that diffuses across the respiratory membrane is similar.

Ventilation is the process that moves air into and out of the alveoli, and perfusion affects the flow of blood in the capillaries. Both are important in gas exchange, as ventilation must be sufficient to create a high partial pressure of oxygen in the alveoli. If ventilation is insufficient and the partial pressure of oxygen drops in the alveolar air, the capillary is constricted and blood flow is redirected to alveoli with sufficient ventilation. External respiration refers to gas exchange that occurs in the alveoli, whereas internal respiration refers to gas exchange that occurs in the tissue. Both are driven by partial pressure differences.

Review Questions

Exercise:

Problem:

Gas moves from an area of _____ partial pressure to an area of _____ partial pressure.

- a. low; high
- b. low; low
- c. high; high
- d. high; low

Solution:

D

Exercise:

Problem:

When ventilation is not sufficient, which of the following occurs?

- a. The capillary constricts.
- b. The capillary dilates.
- c. The partial pressure of oxygen in the affected alveolus increases.
- d. The bronchioles dilate.

Solution:

A

Exercise:

Problem:

Gas exchange that occurs at the level of the tissues is called _____.

- a. external respiration
 - b. interpulmonary respiration
 - c. internal respiration
 - d. pulmonary ventilation
-

Solution:

C

Exercise:

Problem:

The partial pressure of carbon dioxide is 45 mm Hg in the blood and 40 mm Hg in the alveoli. What happens to the carbon dioxide?

- a. It diffuses into the blood.
 - b. It diffuses into the alveoli.
 - c. The gradient is too small for carbon dioxide to diffuse.
 - d. It decomposes into carbon and oxygen.
-

Solution:

B

Critical Thinking Questions

Exercise:

Problem: Compare and contrast Dalton's law and Henry's law.

Solution:

Both Dalton's and Henry's laws describe the behavior of gases. Dalton's law states that any gas in a mixture of gases exerts force as if

it were not in a mixture. Henry's law states that gas molecules dissolve in a liquid proportional to their partial pressure.

Exercise:

Problem:

A smoker develops damage to several alveoli that then can no longer function. How does this affect gas exchange?

Solution:

The damaged alveoli will have insufficient ventilation, causing the partial pressure of oxygen in the alveoli to decrease. As a result, the pulmonary capillaries serving these alveoli will constrict, redirecting blood flow to other alveoli that are receiving sufficient ventilation.

Glossary

Dalton's law

statement of the principle that a specific gas type in a mixture exerts its own pressure, as if that specific gas type was not part of a mixture of gases

external respiration

gas exchange that occurs in the alveoli

Henry's law

statement of the principle that the concentration of gas in a liquid is directly proportional to the solubility and partial pressure of that gas

internal respiration

gas exchange that occurs at the level of body tissues

partial pressure

force exerted by each gas in a mixture of gases

total pressure

sum of all the partial pressures of a gaseous mixture

ventilation

movement of air into and out of the lungs; consists of inspiration and expiration

Transport of Gases

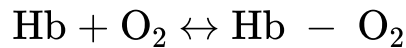
By the end of this section, you will be able to:

- Describe the principles of oxygen transport
- Describe the structure of hemoglobin
- Compare and contrast fetal and adult hemoglobin
- Describe the principles of carbon dioxide transport

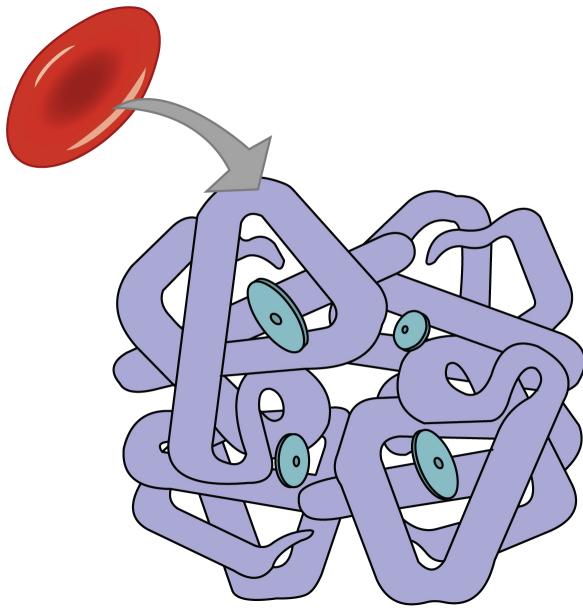
The other major activity in the lungs is the process of respiration, the process of gas exchange. The function of respiration is to provide oxygen for use by body cells during cellular respiration and to eliminate carbon dioxide, a waste product of cellular respiration, from the body. In order for the exchange of oxygen and carbon dioxide to occur, both gases must be transported between the external and internal respiration sites. Although carbon dioxide is more soluble than oxygen in blood, both gases require a specialized transport system for the majority of the gas molecules to be moved between the lungs and other tissues.

Oxygen Transport in the Blood

Even though oxygen is transported via the blood, you may recall that oxygen is not very soluble in liquids. A small amount of oxygen does dissolve in the blood and is transported in the bloodstream, but it is only about 1.5% of the total amount. The majority of oxygen molecules are carried from the lungs to the body's tissues by a specialized transport system, which relies on the erythrocyte—the red blood cell. Erythrocytes contain a metalloprotein, hemoglobin, which serves to bind oxygen molecules to the erythrocyte ([link](#)). Heme is the portion of hemoglobin that contains iron, and it is heme that binds oxygen. One hemoglobin molecule contains iron-containing Heme molecules, and because of this, each hemoglobin molecule is capable of carrying up to four molecules of oxygen. As oxygen diffuses across the respiratory membrane from the alveolus to the capillary, it also diffuses into the red blood cell and is bound by hemoglobin. The following reversible chemical reaction describes the production of the final product, **oxyhemoglobin** (Hb-O_2), which is formed when oxygen binds to hemoglobin. Oxyhemoglobin is a bright red-colored molecule that contributes to the bright red color of oxygenated blood.

Equation:

In this formula, Hb represents reduced hemoglobin, that is, hemoglobin that does not have oxygen bound to it. There are multiple factors involved in how readily heme binds to and dissociates from oxygen, which will be discussed in the subsequent sections.

Erythrocyte and Hemoglobin

Hemoglobin consists of four subunits, each of which contains one molecule of iron.

Function of Hemoglobin

Hemoglobin is composed of subunits, a protein structure that is referred to as a quaternary structure. Each of the four subunits that make up hemoglobin is arranged in a ring-like fashion, with an iron atom covalently bound to the heme in the center of each subunit. Binding of the first oxygen

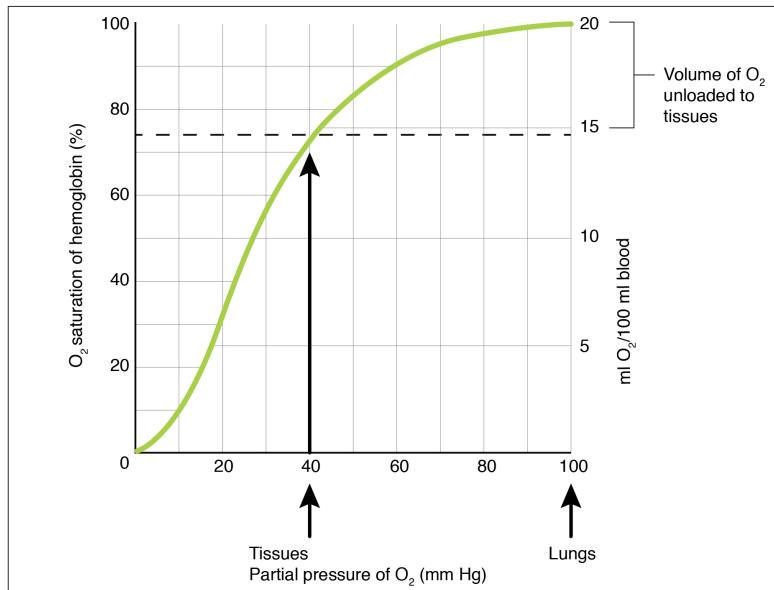
molecule causes a conformational change in hemoglobin that allows the second molecule of oxygen to bind more readily. As each molecule of oxygen is bound, it further facilitates the binding of the next molecule, until all four heme sites are occupied by oxygen. The opposite occurs as well: After the first oxygen molecule dissociates and is “dropped off” at the tissues, the next oxygen molecule dissociates more readily. When all four heme sites are occupied, the hemoglobin is said to be saturated. When one to three heme sites are occupied, the hemoglobin is said to be partially saturated. Therefore, when considering the blood as a whole, the percent of the available heme units that are bound to oxygen at a given time is called hemoglobin saturation. Hemoglobin saturation of 100 percent means that every heme unit in all of the erythrocytes of the body is bound to oxygen. In a healthy individual with normal hemoglobin levels, hemoglobin saturation generally ranges from 95 percent to 99 percent.

Oxygen Dissociation from Hemoglobin

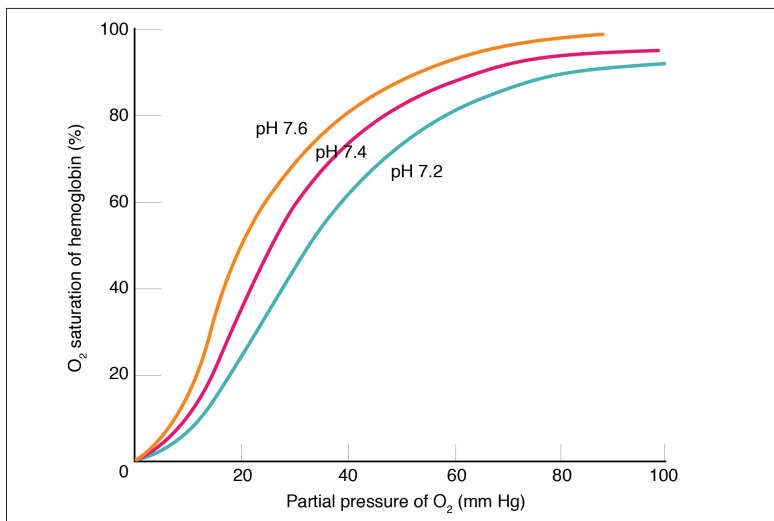
Partial pressure is an important aspect of the binding of oxygen to and disassociation from heme. An **oxygen–hemoglobin dissociation curve** is a graph that describes the relationship of partial pressure to the binding of oxygen to heme and its subsequent dissociation from heme ([\[link\]](#)). Remember that gases travel from an area of higher partial pressure to an area of lower partial pressure. In addition, the affinity of an oxygen molecule for heme increases as more oxygen molecules are bound. Therefore, in the oxygen–hemoglobin saturation curve, as the partial pressure of oxygen increases, a proportionately greater number of oxygen molecules are bound by heme. Not surprisingly, the oxygen–hemoglobin saturation/dissociation curve also shows that the lower the partial pressure of oxygen, the fewer oxygen molecules are bound to heme. As a result, the partial pressure of oxygen plays a major role in determining the degree of binding of oxygen to heme at the site of the respiratory membrane, as well as the degree of dissociation of oxygen from heme at the site of body tissues.

Oxygen-Hemoglobin Dissociation and Effects of pH and Temperature

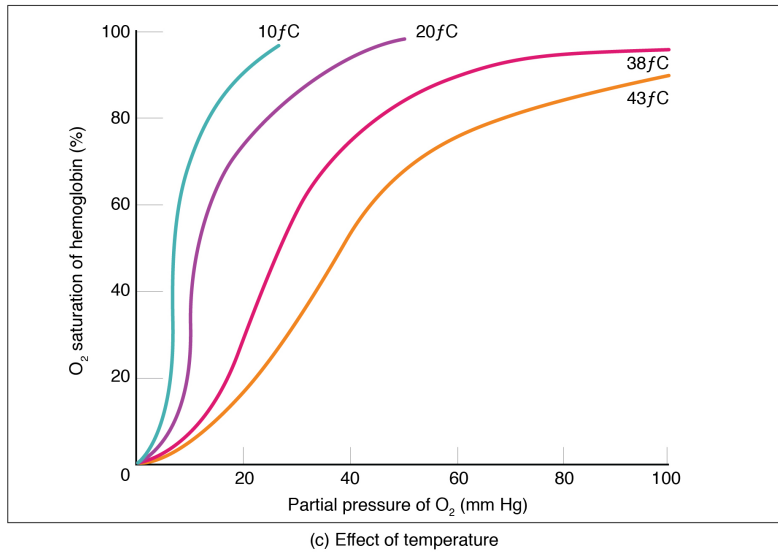
These three graphs show (a) the relationship between the partial pressure of oxygen and hemoglobin saturation, (b) the effect of pH on the oxygen–hemoglobin dissociation curve, and (c) the effect of temperature on the oxygen–hemoglobin dissociation curve.



(a) Partial pressure of oxygen and hemoglobin saturation



(b) Effect of pH



The mechanisms behind the oxygen–hemoglobin saturation/dissociation curve also serve as automatic control mechanisms that regulate how much oxygen is delivered to different tissues throughout the body. This is important because some tissues have a higher metabolic rate than others. Highly active tissues, such as muscle, rapidly use oxygen to produce ATP, lowering the partial pressure of oxygen in the tissue to about 20 mm Hg. The partial pressure of oxygen inside capillaries is about 100 mm Hg, so the difference between the two becomes quite high, about 80 mm Hg. As a result, a greater number of oxygen molecules dissociate from hemoglobin and enter the tissues. The reverse is true of tissues, such as adipose (body fat), which have lower metabolic rates. Because less oxygen is used by these cells, the partial pressure of oxygen within such tissues remains relatively high, resulting in fewer oxygen molecules dissociating from hemoglobin and entering the tissue interstitial fluid. Although venous blood is said to be deoxygenated, some oxygen is still bound to hemoglobin in its red blood cells. This provides an oxygen reserve that can be used when tissues suddenly demand more oxygen.

Factors other than partial pressure also affect the oxygen–hemoglobin saturation/dissociation curve. For example, a higher temperature promotes hemoglobin and oxygen to dissociate faster, whereas a lower temperature inhibits dissociation (see [\[link\]](#), **middle**). However, the human body tightly regulates temperature, so this factor may not affect gas exchange throughout the body. The exception to this is in highly active tissues, which

may release a larger amount of energy than is given off as heat. As a result, oxygen readily dissociates from hemoglobin, which is a mechanism that helps to provide active tissues with more oxygen.

Certain hormones, such as androgens, epinephrine, thyroid hormones, and growth hormone, can affect the oxygen–hemoglobin saturation/dissociation curve by stimulating the production of a compound called 2,3-bisphosphoglycerate (BPG) by erythrocytes. BPG is a byproduct of glycolysis. Because erythrocytes do not contain mitochondria, glycolysis is the sole method by which these cells produce ATP. BPG promotes the disassociation of oxygen from hemoglobin. Therefore, the greater the concentration of BPG, the more readily oxygen dissociates from hemoglobin, despite its partial pressure.

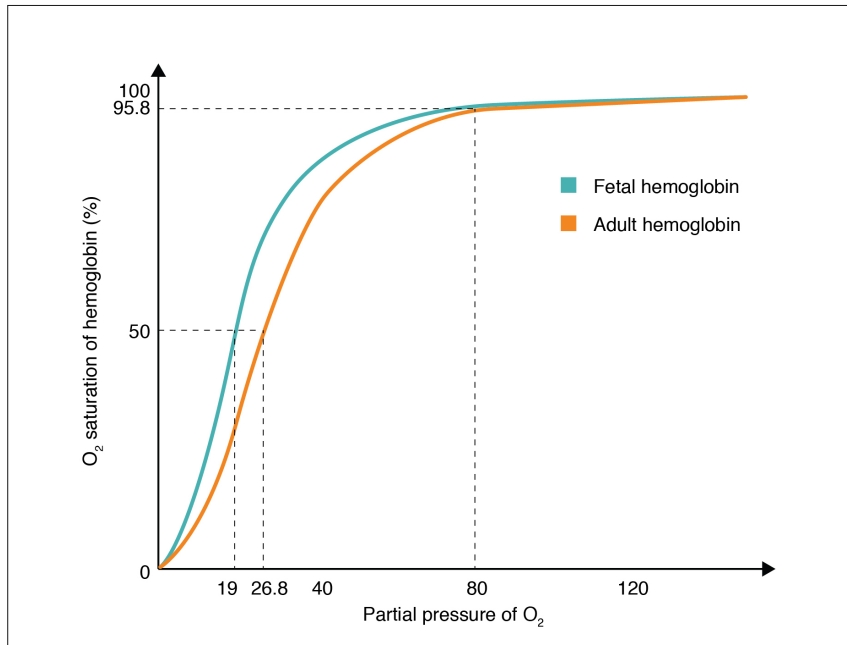
The pH of the blood is another factor that influences the oxygen–hemoglobin saturation/dissociation curve (see [\[link\]](#)). The **Bohr effect** is a phenomenon that arises from the relationship between pH and oxygen's affinity for hemoglobin: A lower, more acidic pH promotes oxygen dissociation from hemoglobin. In contrast, a higher, or more basic, pH inhibits oxygen dissociation from hemoglobin. The greater the amount of carbon dioxide in the blood, the more molecules that must be converted, which in turn generates hydrogen ions and thus lowers blood pH. Furthermore, blood pH may become more acidic when certain byproducts of cell metabolism, such as lactic acid, carbonic acid, and carbon dioxide, are released into the bloodstream.

Hemoglobin of the Fetus

The fetus has its own circulation with its own erythrocytes; however, it is dependent on the mother for oxygen. Blood is supplied to the fetus by way of the umbilical cord, which is connected to the placenta and separated from maternal blood by the chorion. The mechanism of gas exchange at the chorion is similar to gas exchange at the respiratory membrane. However, the partial pressure of oxygen is lower in the maternal blood in the placenta, at about 35 to 50 mm Hg, than it is in maternal arterial blood. The difference in partial pressures between maternal and fetal blood is not large,

as the partial pressure of oxygen in fetal blood at the placenta is about 20 mm Hg. Therefore, there is not as much diffusion of oxygen into the fetal blood supply. The fetus' hemoglobin overcomes this problem by having a greater affinity for oxygen than maternal hemoglobin ([\[link\]](#)). Both fetal and adult hemoglobin have four subunits, but two of the subunits of fetal hemoglobin have a different structure that causes fetal hemoglobin to have a greater affinity for oxygen than does adult hemoglobin.

Oxygen-Hemoglobin Dissociation Curves in Fetus and Adult

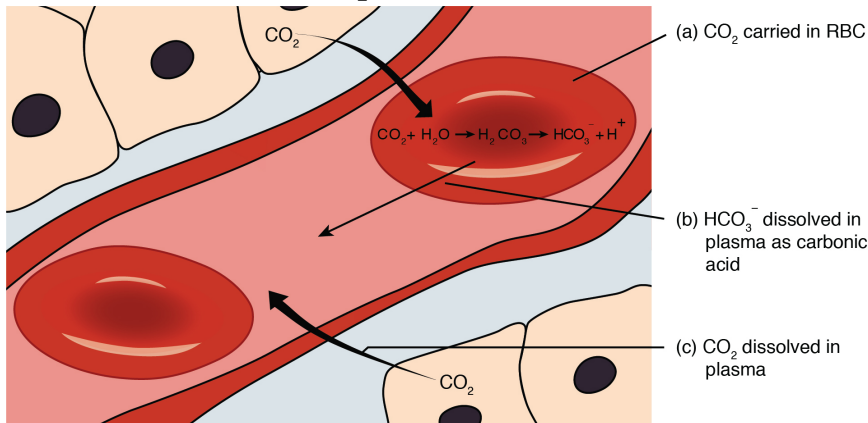


Fetal hemoglobin has a greater affinity for oxygen than does adult hemoglobin.

Carbon Dioxide Transport in the Blood

Carbon dioxide is transported by three major mechanisms. The first mechanism of carbon dioxide transport is by blood plasma, as some carbon dioxide molecules dissolve in the blood. The second mechanism is transport in the form of bicarbonate (HCO_3^-), which also dissolves in plasma. The third mechanism of carbon dioxide transport is similar to the transport of oxygen by erythrocytes ([\[link\]](#)).

Carbon Dioxide Transport



Carbon dioxide is transported by three different methods: (a) in erythrocytes; (b) after forming carbonic acid (H_2CO_3), which is dissolved in plasma; (c) and in plasma.

Dissolved Carbon Dioxide

Although carbon dioxide is not considered to be highly soluble in blood, a small fraction—about 7 to 10 percent—of the carbon dioxide that diffuses into the blood from the tissues dissolves in plasma. The dissolved carbon dioxide then travels in the bloodstream and when the blood reaches the pulmonary capillaries, the dissolved carbon dioxide diffuses across the respiratory membrane into the alveoli, where it is then exhaled during pulmonary ventilation.

Bicarbonate Buffer

A large fraction—about 70 percent—of the carbon dioxide molecules that diffuse into the blood is transported to the lungs as bicarbonate. Most bicarbonate is produced in erythrocytes after carbon dioxide diffuses into the capillaries, and subsequently into red blood cells. **Carbonic anhydrase**

(CA) causes carbon dioxide and water to form carbonic acid (H_2CO_3), which dissociates into two ions: bicarbonate (HCO_3^-) and hydrogen (H^+). The following formula depicts this reaction:

Equation:



Bicarbonate tends to build up in the erythrocytes, so that there is a greater concentration of bicarbonate in the erythrocytes than in the surrounding blood plasma. As a result, some of the bicarbonate will leave the erythrocytes and move down its concentration gradient into the plasma in exchange for chloride (Cl^-) ions. This phenomenon is referred to as the **chloride shift** and occurs because by exchanging one negative ion for another negative ion, neither the electrical charge of the erythrocytes nor that of the blood is altered.

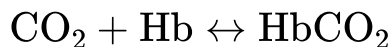
At the pulmonary capillaries, the chemical reaction that produced bicarbonate (shown above) is reversed, and carbon dioxide and water are the products. Much of the bicarbonate in the plasma re-enters the erythrocytes in exchange for chloride ions. Hydrogen ions and bicarbonate ions join to form carbonic acid, which is converted into carbon dioxide and water by carbonic anhydrase. Carbon dioxide diffuses out of the erythrocytes and into the plasma, where it can further diffuse across the respiratory membrane into the alveoli to be exhaled during pulmonary ventilation.

Carbaminohemoglobin

About 20 percent of carbon dioxide is bound by hemoglobin and is transported to the lungs. Carbon dioxide does not bind to iron as oxygen does; instead, carbon dioxide binds amino acid moieties on the globin portions of hemoglobin to form **carbaminohemoglobin**, which forms when hemoglobin and carbon dioxide bind. When hemoglobin is not transporting oxygen, it tends to have a bluish-purple tone to it, creating the darker

maroon color typical of deoxygenated blood. The following formula depicts this reversible reaction:

Equation:



Similar to the transport of oxygen by heme, the binding and dissociation of carbon dioxide to and from hemoglobin is dependent on the partial pressure of carbon dioxide. Because carbon dioxide is released from the lungs, blood that leaves the lungs and reaches body tissues has a lower partial pressure of carbon dioxide than is found in the tissues. As a result, carbon dioxide leaves the tissues because of its higher partial pressure, enters the blood, and then moves into red blood cells, binding to hemoglobin. In contrast, in the pulmonary capillaries, the partial pressure of carbon dioxide is high compared to within the alveoli. As a result, carbon dioxide dissociates readily from hemoglobin and diffuses across the respiratory membrane into the air.

In addition to the partial pressure of carbon dioxide, the oxygen saturation of hemoglobin and the partial pressure of oxygen in the blood also influence the affinity of hemoglobin for carbon dioxide. The **Haldane effect** is a phenomenon that arises from the relationship between the partial pressure of oxygen and the affinity of hemoglobin for carbon dioxide. Hemoglobin that is saturated with oxygen does not readily bind carbon dioxide. However, when oxygen is not bound to heme and the partial pressure of oxygen is low, hemoglobin readily binds to carbon dioxide.

Note:



Watch this [video](#) to see the transport of oxygen from the lungs to the tissues. Why is oxygenated blood bright red, whereas deoxygenated blood tends to be more of a purple color?

Chapter Review

Oxygen is primarily transported through the blood by erythrocytes. These cells contain a metalloprotein called hemoglobin, which is composed of four subunits with a ring-like structure. Each subunit contains one atom of iron bound to a molecule of heme. Heme binds oxygen so that each hemoglobin molecule can bind up to four oxygen molecules. When all of the heme units in the blood are bound to oxygen, hemoglobin is considered to be saturated. Hemoglobin is partially saturated when only some heme units are bound to oxygen. An oxygen–hemoglobin saturation/dissociation curve is a common way to depict the relationship of how easily oxygen binds to or dissociates from hemoglobin as a function of the partial pressure of oxygen. As the partial pressure of oxygen increases, the more readily hemoglobin binds to oxygen. At the same time, once one molecule of oxygen is bound by hemoglobin, additional oxygen molecules more readily bind to hemoglobin. Other factors such as temperature, pH, the partial pressure of carbon dioxide, and the concentration of 2,3-bisphosphoglycerate can enhance or inhibit the binding of hemoglobin and oxygen as well. Fetal hemoglobin has a different structure than adult hemoglobin, which results in fetal hemoglobin having a greater affinity for oxygen than adult hemoglobin.

Carbon dioxide is transported in blood by three different mechanisms: as dissolved carbon dioxide, as bicarbonate, or as carbaminohemoglobin. A small portion of carbon dioxide remains. The largest amount of transported carbon dioxide is as bicarbonate, formed in erythrocytes. For this conversion, carbon dioxide is combined with water with the aid of an enzyme called carbonic anhydrase. This combination forms carbonic acid, which spontaneously dissociates into bicarbonate and hydrogen ions. As bicarbonate builds up in erythrocytes, it is moved across the membrane into the plasma in exchange for chloride ions by a mechanism called the

chloride shift. At the pulmonary capillaries, bicarbonate re-enters erythrocytes in exchange for chloride ions, and the reaction with carbonic anhydrase is reversed, recreating carbon dioxide and water. Carbon dioxide then diffuses out of the erythrocyte and across the respiratory membrane into the air. An intermediate amount of carbon dioxide binds directly to hemoglobin to form carbaminohemoglobin. The partial pressures of carbon dioxide and oxygen, as well as the oxygen saturation of hemoglobin, influence how readily hemoglobin binds carbon dioxide. The less saturated hemoglobin is and the lower the partial pressure of oxygen in the blood is, the more readily hemoglobin binds to carbon dioxide. This is an example of the Haldane effect.

Interactive Link Questions

Exercise:

Problem:

Watch this [video](#) to see the transport of oxygen from the lungs to the tissues. Why is oxygenated blood bright red, whereas deoxygenated blood tends to be more of a purple color?

Solution:

When oxygen binds to the hemoglobin molecule, oxyhemoglobin is created, which has a red color to it. Hemoglobin that is not bound to oxygen tends to be more of a blue–purple color. Oxygenated blood traveling through the systemic arteries has large amounts of oxyhemoglobin. As blood passes through the tissues, much of the oxygen is released into systemic capillaries. The deoxygenated blood returning through the systemic veins, therefore, contains much smaller amounts of oxyhemoglobin. The more oxyhemoglobin that is present in the blood, the redder the fluid will be. As a result, oxygenated blood will be much redder in color than deoxygenated blood.

Review Questions

Exercise:

Problem:

Oxyhemoglobin forms by a chemical reaction between which of the following?

- a. hemoglobin and carbon dioxide
- b. carbonic anhydrase and carbon dioxide
- c. hemoglobin and oxygen
- d. carbonic anhydrase and oxygen

Solution:

C

Exercise:

Problem:

Which of the following factors play a role in the oxygen–hemoglobin saturation/dissociation curve?

- a. temperature
- b. pH
- c. BPG
- d. all of the above

Solution:

D

Exercise:

Problem: Which of the following occurs during the chloride shift?

- a. Chloride is removed from the erythrocyte.
- b. Chloride is exchanged for bicarbonate.

- c. Bicarbonate is removed from the erythrocyte.
 - d. Bicarbonate is removed from the blood.
-

Solution:

B

Exercise:

Problem:

A low partial pressure of oxygen promotes hemoglobin binding to carbon dioxide. This is an example of the _____.

- a. Haldane effect
 - b. Bohr effect
 - c. Dalton's law
 - d. Henry's law
-

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

Compare and contrast adult hemoglobin and fetal hemoglobin.

Solution:

Both adult and fetal hemoglobin transport oxygen via iron molecules. However, fetal hemoglobin has about a 20-fold greater affinity for oxygen than does adult hemoglobin. This is due to a difference in

structure; fetal hemoglobin has two subunits that have a slightly different structure than the subunits of adult hemoglobin.

Exercise:

Problem:

Describe the relationship between the partial pressure of oxygen and the binding of oxygen to hemoglobin.

Solution:

The relationship between the partial pressure of oxygen and the binding of hemoglobin to oxygen is described by the oxygen–hemoglobin saturation/dissociation curve. As the partial pressure of oxygen increases, the number of oxygen molecules bound by hemoglobin increases, thereby increasing the saturation of hemoglobin.

Exercise:

Problem:

Describe three ways in which carbon dioxide can be transported.

Solution:

Carbon dioxide can be transported by three mechanisms: dissolved in plasma, as bicarbonate, or as carbaminohemoglobin. Dissolved in plasma, carbon dioxide molecules simply diffuse into the blood from the tissues. Bicarbonate is created by a chemical reaction that occurs mostly in erythrocytes, joining carbon dioxide and water by carbonic anhydrase, producing carbonic acid, which breaks down into bicarbonate and hydrogen ions. Carbaminohemoglobin is the bound form of hemoglobin and carbon dioxide.

Glossary

Bohr effect

relationship between blood pH and oxygen dissociation from hemoglobin

carbaminohemoglobin

bound form of hemoglobin and carbon dioxide

carbonic anhydrase (CA)

enzyme that catalyzes the reaction that causes carbon dioxide and water to form carbonic acid

chloride shift

facilitated diffusion that exchanges bicarbonate (HCO_3^-) with chloride (Cl^-) ions

Haldane effect

relationship between the partial pressure of oxygen and the affinity of hemoglobin for carbon dioxide

oxyhemoglobin

(Hb-O_2) bound form of hemoglobin and oxygen

oxygen–hemoglobin dissociation curve

graph that describes the relationship of partial pressure to the binding and disassociation of oxygen to and from heme

Modifications in Respiratory Functions

By the end of this section, you will be able to:

- Define the terms hyperpnea and hyperventilation
- Describe the effect of exercise on the respiratory system
- Describe the effect of high altitude on the respiratory system
- Discuss the process of acclimatization

At rest, the respiratory system performs its functions at a constant, rhythmic pace, as regulated by the respiratory centers of the brain. At this pace, ventilation provides sufficient oxygen to all the tissues of the body.

However, there are times that the respiratory system must alter the pace of its functions in order to accommodate the oxygen demands of the body.

Hyperpnea

Hyperpnea is an increased depth and rate of ventilation to meet an increase in oxygen demand as might be seen in exercise or disease, particularly diseases that target the respiratory or digestive tracts. This does not significantly alter blood oxygen or carbon dioxide levels, but merely increases the depth and rate of ventilation to meet the demand of the cells.

In contrast, **hyperventilation** is an increased ventilation rate that is independent of the cellular oxygen needs and leads to abnormally low blood carbon dioxide levels and high (alkaline) blood pH.

Interestingly, exercise does not cause hyperpnea as one might think. Muscles that perform work during exercise do increase their demand for oxygen, stimulating an increase in ventilation. However, hyperpnea during exercise appears to occur before a drop in oxygen levels within the muscles can occur. Therefore, hyperpnea must be driven by other mechanisms, either instead of or in addition to a drop in oxygen levels. The exact mechanisms behind exercise hyperpnea are not well understood, and some hypotheses are somewhat controversial. However, in addition to low oxygen, high carbon dioxide, and low pH levels, there appears to be a complex interplay of factors related to the nervous system and the respiratory centers of the brain.

First, a conscious decision to partake in exercise, or another form of physical exertion, results in a psychological stimulus that may trigger the respiratory centers of the brain to increase ventilation. In addition, the respiratory centers of the brain may be stimulated through the activation of motor neurons that innervate muscle groups that are involved in the physical activity. Finally, physical exertion stimulates proprioceptors, which are receptors located within the muscles, joints, and tendons, which sense movement and stretching; proprioceptors thus create a stimulus that may also trigger the respiratory centers of the brain. These neural factors are consistent with the sudden increase in ventilation that is observed immediately as exercise begins. Because the respiratory centers are stimulated by psychological, motor neuron, and proprioceptor inputs throughout exercise, the fact that there is also a sudden decrease in ventilation immediately after the exercise ends when these neural stimuli cease, further supports the idea that they are involved in triggering the changes of ventilation.

High Altitude Effects

An increase in altitude results in a decrease in atmospheric pressure. Although the proportion of oxygen relative to gases in the atmosphere remains at 21 percent, its partial pressure decreases ([\[link\]](#)). As a result, it is more difficult for a body to achieve the same level of oxygen saturation at high altitude than at low altitude, due to lower atmospheric pressure. In fact, hemoglobin saturation is lower at high altitudes compared to hemoglobin saturation at sea level. For example, hemoglobin saturation is about 67 percent at 19,000 feet above sea level, whereas it reaches about 98 percent at sea level.

Partial Pressure of Oxygen at Different Altitudes

| Partial Pressure of Oxygen at Different Altitudes | | | Partial pressure of oxygen (mm Hg) |
|--|--|-------------------------------------|---|
| Example location | Altitude (feet above sea level) | Atmospheric pressure (mm Hg) | Partial pressure of oxygen (mm Hg) |
| Example location | Altitude (feet above sea level) | Atmospheric pressure (mm Hg) | Partial pressure of oxygen (mm Hg) |
| New York City, New York | 0 | 760 | 159 |
| Boulder, Colorado | 5000 | 632 | 133 |
| Aspen, Colorado | 8000 | 565 | 118 |
| Pike's Peak, Colorado | 14,000 | 447 | 94 |
| Denali (Mt. McKinley), Alaska | 20,000 | 350 | 73 |
| Mt. Everest, Tibet | 29,000 | 260 | 54 |

As you recall, partial pressure is extremely important in determining how much gas can cross the respiratory membrane and enter the blood of the pulmonary capillaries. A lower partial pressure of oxygen means that there is a smaller difference in partial pressures between the alveoli and the blood, so less oxygen crosses the respiratory membrane. As a result, fewer oxygen molecules are bound by hemoglobin. Despite this, the tissues of the body still receive a sufficient amount of oxygen during rest at high

altitudes. This is due to two major mechanisms. First, the number of oxygen molecules that enter the tissue from the blood is nearly equal between sea level and high altitudes. At sea level, hemoglobin saturation is higher, but only a quarter of the oxygen molecules are actually released into the tissue. At high altitudes, a greater proportion of molecules of oxygen are released into the tissues. Secondly, at high altitudes, a greater amount of BPG is produced by erythrocytes, which enhances the dissociation of oxygen from hemoglobin. Physical exertion, such as skiing or hiking, can lead to altitude sickness due to the low amount of oxygen reserves in the blood at high altitudes. At sea level, there is a large amount of oxygen reserve in venous blood (even though venous blood is thought of as “deoxygenated”) from which the muscles can draw during physical exertion. Because the oxygen saturation is much lower at higher altitudes, this venous reserve is small, resulting in pathological symptoms of low blood oxygen levels. You may have heard that it is important to drink more water when traveling at higher altitudes than you are accustomed to. This is because your body will increase micturition (urination) at high altitudes to counteract the effects of lower oxygen levels. By removing fluids, blood plasma levels drop but not the total number of erythrocytes. In this way, the overall concentration of erythrocytes in the blood increases, which helps tissues obtain the oxygen they need.

Acute mountain sickness (AMS), or altitude sickness, is a condition that results from acute exposure to high altitudes due to a low partial pressure of oxygen at high altitudes. AMS typically can occur at 2400 meters (8000 feet) above sea level. AMS is a result of low blood oxygen levels, as the body has acute difficulty adjusting to the low partial pressure of oxygen. In serious cases, AMS can cause pulmonary or cerebral edema. Symptoms of AMS include nausea, vomiting, fatigue, lightheadedness, drowsiness, feeling disoriented, increased pulse, and nosebleeds. The only treatment for AMS is descending to a lower altitude; however, pharmacologic treatments and supplemental oxygen can improve symptoms. AMS can be prevented by slowly ascending to the desired altitude, allowing the body to acclimate, as well as maintaining proper hydration.

Acclimatization

Especially in situations where the ascent occurs too quickly, traveling to areas of high altitude can cause AMS. **Acclimatization** is the process of adjustment that the respiratory system makes due to chronic exposure to a high altitude. Over a period of time, the body adjusts to accommodate the lower partial pressure of oxygen. The low partial pressure of oxygen at high altitudes results in a lower oxygen saturation level of hemoglobin in the blood. In turn, the tissue levels of oxygen are also lower. As a result, the kidneys are stimulated to produce the hormone erythropoietin (EPO), which stimulates the production of erythrocytes, resulting in a greater number of circulating erythrocytes in an individual at a high altitude over a long period. With more red blood cells, there is more hemoglobin to help transport the available oxygen. Even though there is low saturation of each hemoglobin molecule, there will be more hemoglobin present, and therefore more oxygen in the blood. Over time, this allows the person to partake in physical exertion without developing AMS.

Chapter Review

Normally, the respiratory centers of the brain maintain a consistent, rhythmic breathing cycle. However, in certain cases, the respiratory system must adjust to situational changes in order to supply the body with sufficient oxygen. For example, exercise results in increased ventilation, and chronic exposure to a high altitude results in a greater number of circulating erythrocytes. Hyperpnea, an increase in the rate and depth of ventilation, appears to be a function of three neural mechanisms that include a psychological stimulus, motor neuron activation of skeletal muscles, and the activation of proprioceptors in the muscles, joints, and tendons. As a result, hyperpnea related to exercise is initiated when exercise begins, as opposed to when tissue oxygen demand actually increases.

In contrast, acute exposure to a high altitude, particularly during times of physical exertion, does result in low blood and tissue levels of oxygen. This change is caused by a low partial pressure of oxygen in the air, because the atmospheric pressure at high altitudes is lower than the atmospheric pressure at sea level. This can lead to a condition called acute mountain sickness (AMS) with symptoms that include headaches, disorientation, fatigue, nausea, and lightheadedness. Over a long period of time, a person's

body will adjust to the high altitude, a process called acclimatization. During acclimatization, the low tissue levels of oxygen will cause the kidneys to produce greater amounts of the hormone erythropoietin, which stimulates the production of erythrocytes. Increased levels of circulating erythrocytes provide an increased amount of hemoglobin that helps supply an individual with more oxygen, preventing the symptoms of AMS.

Review Questions

Exercise:

Problem:

Increased ventilation that results in an increase in blood pH is called _____.

- a. hyperventilation
- b. hyperpnea
- c. acclimatization
- d. apnea

Solution:

A

Exercise:

Problem:

Exercise can trigger symptoms of AMS due to which of the following?

- a. low partial pressure of oxygen
- b. low atmospheric pressure
- c. abnormal neural signals
- d. small venous reserve of oxygen

Solution:

D

Exercise:

Problem:

Which of the following stimulates the production of erythrocytes?

- a. AMS
- b. high blood levels of carbon dioxide
- c. low atmospheric pressure
- d. erythropoietin

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

Describe the neural factors involved in increasing ventilation during exercise.

Solution:

There are three neural factors that play a role in the increased ventilation observed during exercise. Because this increased ventilation occurs at the beginning of exercise, it is unlikely that only blood oxygen and carbon dioxide levels are involved. The first neural factor is the psychological stimulus of making a conscious decision to exercise. The second neural factor is the stimulus of motor neuron activation by the skeletal muscles, which are involved in exercise. The third neural factor is activation of the proprioceptors located in the muscles, joints, and tendons that stimulate activity in the respiratory centers.

Exercise:

Problem: What is the major mechanism that results in acclimatization?

Solution:

A major mechanism involved in acclimatization is the increased production of erythrocytes. A drop in tissue levels of oxygen stimulates the kidneys to produce the hormone erythropoietin, which signals the bone marrow to produce erythrocytes. As a result, individuals exposed to a high altitude for long periods of time have a greater number of circulating erythrocytes than do individuals at lower altitudes.

Glossary

acute mountain sickness (AMS)

condition that occurs as a result of acute exposure to high altitude due to a low partial pressure of oxygen

acclimatization

process of adjustment that the respiratory system makes due to chronic exposure to high altitudes

hyperpnea

increased rate and depth of ventilation due to an increase in oxygen demand that does not significantly alter blood oxygen or carbon dioxide levels

hyperventilation

increased ventilation rate that leads to abnormally low blood carbon dioxide levels and high (alkaline) blood pH

Introduction
class="introduction"
Sewage Treatment Plant

(credit:
“eutrophication&hypoxia”/flickr.com
)



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Describe the composition of urine
- Label structures of the urinary system
- Characterize the roles of each of the parts of the urinary system

- Illustrate the macroscopic and microscopic structures of the kidney
- Trace the flow of blood through the kidney
- Outline how blood is filtered in the kidney nephron
- Provide symptoms of kidney failure
- List some of the solutes filtered, secreted, and reabsorbed in different parts of the nephron
- Describe the role of a portal system in the kidney
- Explain how urine osmolarity is hormonally regulated
- Describe the regulation of major ions by the kidney
- Summarize the role of the kidneys in maintaining acid–base balance

The urinary system has roles you may be well aware of: cleansing the blood and ridding the body of wastes probably come to mind. However, there are additional, equally important functions played by the system. Take for example, regulation of pH, a function shared with the lungs and the buffers in the blood. Additionally, the regulation of blood pressure is a role shared with the heart and blood vessels. What about regulating the concentration of solutes in the blood? Did you know that the kidney is important in determining the concentration of red blood cells? Eighty-five percent of the erythropoietin (EPO) produced to stimulate red blood cell production is produced in the kidneys. The kidneys also perform the final synthesis step of vitamin D production, converting calcidiol to calcitriol, the active form of vitamin D.

If the kidneys fail, these functions are compromised or lost altogether, with devastating effects on homeostasis. The affected individual might experience weakness, lethargy, shortness of breath, anemia, widespread edema (swelling), metabolic acidosis, rising potassium levels, heart arrhythmias, and more. Each of these functions is vital to your well-being and survival. The urinary system, controlled by the nervous system, also stores urine until a convenient time for disposal and then provides the anatomical structures to transport this waste liquid to the outside of the body. Failure of nervous control or the anatomical structures leading to a loss of control of urination results in a condition called incontinence.

This chapter will help you to understand the anatomy of the urinary system and how it enables the physiologic functions critical to homeostasis. It is best to think of the kidney as a regulator of plasma makeup rather than simply a urine producer. As you read each section, ask yourself this question: “What happens if this does not work?” This question will help you to understand how the urinary system maintains homeostasis and affects all the other systems of the body and the quality of one’s life.

Note:



Watch this [video](#) from the Howard Hughes Medical Institute for an introduction to the urinary system.

Physical Characteristics of Urine

By the end of this section, you will be able to:

- Compare and contrast blood plasma, glomerular filtrate, and urine characteristics
- Describe the characteristics of a normal urine sample, including normal range of pH, osmolarity, and volume

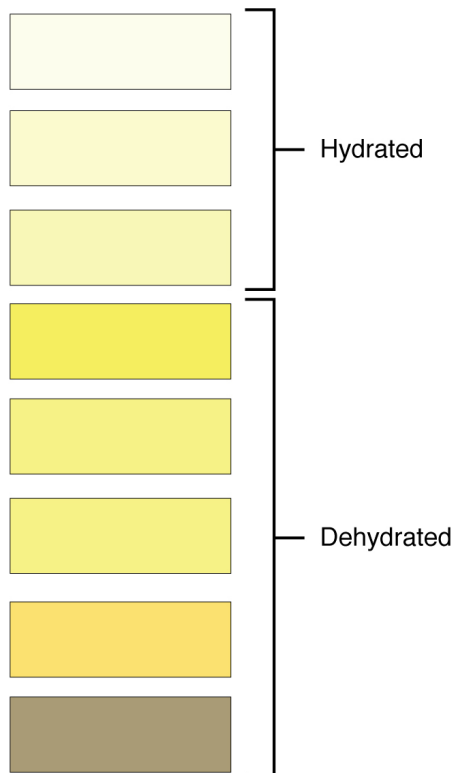
The urinary system's ability to filter the blood resides in about 2 to 3 million tufts of specialized capillaries—the glomeruli—distributed more or less equally between the two kidneys. Because the glomeruli filter the blood based mostly on particle size, large elements like blood cells, platelets, antibodies, and albumen are excluded. The glomerulus is the first part of the nephron, which then continues as a highly specialized tubular structure responsible for creating the final urine composition. All other solutes, such as ions, amino acids, vitamins, and wastes, are filtered to create a filtrate composition very similar to plasma. The glomeruli create about 200 liters (189 quarts) of this filtrate every day, yet you excrete less than two liters of waste you call urine.

Characteristics of the urine change, depending on influences such as water intake, exercise, environmental temperature, nutrient intake, and other factors ([\[link\]](#)). Some of the characteristics such as color and odor are rough descriptors of your state of hydration. For example, if you exercise or work outside, and sweat a great deal, your urine will turn darker and produce a slight odor, even if you drink plenty of water. Athletes are often advised to consume water until their urine is clear. This is good advice; however, it takes time for the kidneys to process body fluids and store it in the bladder. Another way of looking at this is that the quality of the urine produced is an average over the time it takes to make that urine. Producing clear urine may take only a few minutes if you are drinking a lot of water or several hours if you are working outside and not drinking much.

| Normal Urine Characteristics | |
|-------------------------------------|--|
| Characteristic | Normal values |
| Color | Pale yellow to deep amber |
| Odor | Odorless |
| Volume | 750–2000 mL/24 hour |
| pH | 4.5–8.0 |
| Specific gravity | 1.003–1.032 |
| Osmolarity | 40–1350 mOsmol/kg |
| Urobilinogen | 0.2–1.0 mg/100 mL |
| White blood cells | 0–2 HPF (per high-power field of microscope) |
| Leukocyte esterase | None |
| Protein | None or trace |
| Bilirubin | <0.3 mg/100 mL |
| Ketones | None |
| Nitrites | None |
| Blood | None |
| Glucose | None |

Urinalysis (urine analysis) often provides clues to renal disease. Normally, only traces of protein are found in urine, and when higher amounts are found, damage to the glomeruli is the likely basis. Unusually large quantities of urine may point to diseases like diabetes mellitus or hypothalamic tumors that cause diabetes insipidus. The color of urine is determined mostly by the breakdown products of red blood cell destruction ([link](#)). The “heme” of hemoglobin is converted by the liver into water-soluble forms that can be excreted into the bile and indirectly into the urine. This yellow pigment is **urochrome**. Urine color may also be affected by certain foods like beets, berries, and fava beans. A kidney stone or a cancer of the urinary system may produce sufficient bleeding to manifest as pink or even bright red urine. Diseases of the liver or obstructions of bile drainage from the liver impart a dark “tea” or “cola” hue to the urine. Dehydration produces darker, concentrated urine that may also possess the slight odor of ammonia. Most of the ammonia produced from protein breakdown is converted into urea by the liver, so ammonia is rarely detected in fresh urine. The strong ammonia odor you may detect in bathrooms or alleys is due to the breakdown of urea into ammonia by bacteria in the environment. About one in five people detect a distinctive odor in their urine after consuming asparagus; other foods such as onions, garlic, and fish can impart their own aromas! These food-caused odors are harmless.

Urine Color



Urine volume varies considerably. The normal range is one to two liters per day ([\[link\]](#)). The kidneys must produce a minimum urine volume of about 500 mL/day to rid the body of wastes. Output below this level may be caused by severe dehydration or renal disease and is termed **oliguria**. The virtual absence of urine production is termed **anuria**. Excessive urine production is **polyuria**, which may be due to diabetes mellitus or diabetes insipidus. In diabetes mellitus, blood glucose levels exceed the number of available sodium-glucose transporters in the kidney, and glucose appears in the urine. The osmotic nature of glucose attracts water, leading to its loss in the urine. In the case of diabetes insipidus, insufficient pituitary antidiuretic hormone (ADH) release or insufficient numbers of ADH receptors in the collecting ducts means that too few water channels are inserted into the cell membranes that line the collecting ducts of the kidney. Insufficient numbers of water channels (aquaporins) reduce water absorption, resulting in high volumes of very dilute urine.

| Urine Volumes | | |
|------------------|----------------|---|
| Volume condition | Volume | Causes |
| Normal | 1–2 L/day | |
| Polyuria | >2.5 L/day | Diabetes mellitus; diabetes insipidus; excess caffeine or alcohol; kidney disease; certain drugs, such as diuretics; sickle cell anemia; excessive water intake |
| Oliguria | 300–500 mL/day | Dehydration; blood loss; diarrhea; cardiogenic shock; kidney disease; enlarged prostate |
| Anuria | <50 mL/day | Kidney failure; obstruction, such as kidney stone or tumor; enlarged prostate |

The pH (hydrogen ion concentration) of the urine can vary more than 1000-fold, from a normal low of 4.5 to a maximum of 8.0. Diet can influence pH; meats lower the pH, whereas citrus fruits, vegetables, and dairy products raise the pH. Chronically high or low pH can lead to disorders, such as the development of kidney stones or osteomalacia.

Specific gravity is a measure of the quantity of solutes per unit volume of a solution and is traditionally easier to measure than osmolarity. Urine will always have a specific gravity greater than pure water (water = 1.0) due to the presence of solutes. Laboratories can now measure urine osmolarity directly, which is a more accurate indicator of urinary solutes than **specific gravity**. Remember that osmolarity is the number of osmoles or milliosmoles per liter of fluid (mOsmol/L). Urine osmolarity ranges from a low of 50–100 mOsmol/L to as high as 1200 mOsmol/L H₂O.

Cells are not normally found in the urine. The presence of leukocytes may indicate a urinary tract infection. **Leukocyte esterase** is released by leukocytes; if detected in the urine, it can be taken as indirect evidence of a urinary tract infection (UTI).

Protein does not normally leave the glomerular capillaries, so only trace amounts of protein should be found in the urine, approximately 10 mg/100 mL in a random sample. If excessive protein is detected in the urine, it usually means that the glomerulus is damaged and is allowing protein to “leak” into the filtrate.

Ketones are byproducts of fat metabolism. Finding ketones in the urine suggests that the body is using fat as an energy source in preference to glucose. In diabetes mellitus when there is not enough insulin (type I diabetes mellitus) or because of insulin resistance (type II diabetes mellitus), there is plenty of glucose, but without the action of insulin, the cells cannot take it up, so it remains in the bloodstream. Instead, the cells are forced to use fat as their energy source, and fat consumed at such a level produces excessive ketones as byproducts. These excess ketones will appear in the urine. Ketones may also appear if there is a severe deficiency of proteins or carbohydrates in the diet.

Nitrates (NO_3^-) occur normally in the urine. Gram-negative bacteria metabolize nitrate into nitrite (NO_2^-), and its presence in the urine is indirect evidence of infection.

There should be no blood found in the urine. It may sometimes appear in urine samples as a result of menstrual contamination, but this is not an abnormal condition. Now that you understand what the normal characteristics of urine are, the next section will introduce you to how you store and dispose of this waste product and how you make it.

Chapter Review

The kidney glomerulus filters blood mainly based on particle size to produce a filtrate lacking cells or large proteins. Most of the ions and molecules in the filtrate are needed by the body and must be reabsorbed

farther down the nephron tubules, resulting in the formation of urine. Urine characteristics change depending on water intake, exercise, environmental temperature, and nutrient intake. Urinalysis analyzes characteristics of the urine and is used to diagnose diseases. A minimum of 400 to 500 mL urine must be produced daily to rid the body of wastes. Excessive quantities of urine may indicate diabetes insipidus or diabetes mellitus. The pH range of urine is 4.5 to 8.0, and is affected by diet. Osmolarity ranges from 50 to 1200 milliosmoles, and is a reflection of the amount of water being recovered or lost by renal nephrons.

Review Questions

Exercise:

Problem:

Diabetes insipidus or diabetes mellitus would most likely be indicated by _____.

- a. anuria
- b. polyuria
- c. oliguria
- d. none of the above

Solution:

B

Exercise:

Problem: The color of urine is determined mainly by _____.

- a. diet
 - b. filtration rate
 - c. byproducts of red blood cell breakdown
 - d. filtration efficiency
-

Solution:

C

Exercise:

Problem:

Production of less than 50 mL/day of urine is called _____.

- a. normal
- b. polyuria
- c. oliguria
- d. anuria

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

What is suggested by the presence of white blood cells found in the urine?

Solution:

The presence of white blood cells found in the urine suggests urinary tract infection.

Exercise:

Problem:

Both diabetes mellitus and diabetes insipidus produce large urine volumes, but how would other characteristics of the urine differ between the two diseases?

Solution:

Diabetes mellitus would result in urine containing glucose, and diabetes insipidus would produce urine with very low osmolarity (low specific gravity, dilute).

Glossary

anuria

absence of urine produced; production of 50 mL or less per day

leukocyte esterase

enzyme produced by leukocytes that can be detected in the urine and that serves as an indirect indicator of urinary tract infection

oliguria

below normal urine production of 400–500 mL/day

polyuria

urine production in excess of 2.5 L/day; may be caused by diabetes insipidus, diabetes mellitus, or excessive use of diuretics

specific gravity

weight of a liquid compared to pure water, which has a specific gravity of 1.0; any solute added to water will increase its specific gravity

urinalysis

analysis of urine to diagnose disease

urochrome

heme-derived pigment that imparts the typical yellow color of urine

Gross Anatomy of Urine Transport

By the end of this section, you will be able to:

- Identify the ureters, urinary bladder, and urethra, as well as their location, structure, histology, and function
- Compare and contrast male and female urethras
- Describe the micturition reflex
- Describe voluntary and involuntary neural control of micturition

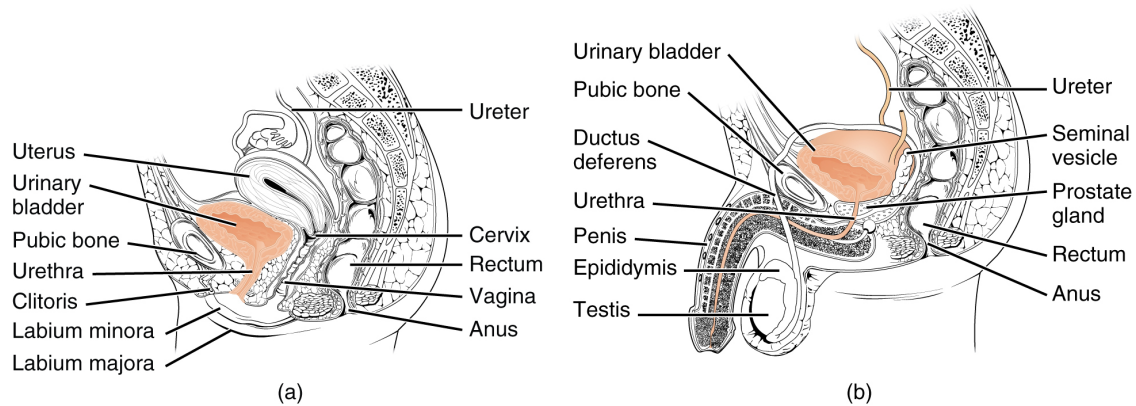
Rather than start with urine formation, this section will start with urine excretion. Urine is a fluid of variable composition that requires specialized structures to remove it from the body safely and efficiently. Blood is filtered, and the filtrate is transformed into urine at a relatively constant rate throughout the day. This processed liquid is stored until a convenient time for excretion. All structures involved in the transport and storage of the urine are large enough to be visible to the naked eye. This transport and storage system not only stores the waste, but it protects the tissues from damage due to the wide range of pH and osmolarity of the urine, prevents infection by foreign organisms, and for the male, provides reproductive functions.

Urethra

The **urethra** transports urine from the bladder to the outside of the body for disposal. The urethra is the only urologic organ that shows any significant anatomic difference between males and females; all other urine transport structures are identical ([\[link\]](#)).

Female and Male Urethras

The urethra transports urine from the bladder to the outside of the body. This image shows (a) a female urethra and (b) a male urethra.



The urethra in both males and females begins inferior and central to the two ureteral openings forming the three points of a triangular-shaped area at the base of the bladder called the **trigone** (Greek tri- = “triangle” and the root of the word “trigonometry”). The urethra tracks posterior and inferior to the pubic symphysis (see [\[link\]](#)**a**). In both males and females, the proximal urethra is lined by transitional epithelium, whereas the terminal portion is a nonkeratinized, stratified squamous epithelium. In the male, pseudostratified columnar epithelium lines the urethra between these two cell types. Voiding is regulated by an involuntary autonomic nervous system-controlled **internal urinary sphincter**, consisting of smooth muscle and voluntary skeletal muscle that forms the **external urinary sphincter** below it.

Female Urethra

The external urethral orifice is embedded in the anterior vaginal wall inferior to the clitoris, superior to the vaginal opening (introitus), and medial to the labia minora. Its short length, about 4 cm, is less of a barrier to fecal bacteria than the longer male urethra and the best explanation for the greater incidence of UTI in women. Voluntary control of the external urethral sphincter is a function of the pudendal nerve. It arises in the sacral region of the spinal cord, traveling via the S2–S4 nerves of the sacral plexus.

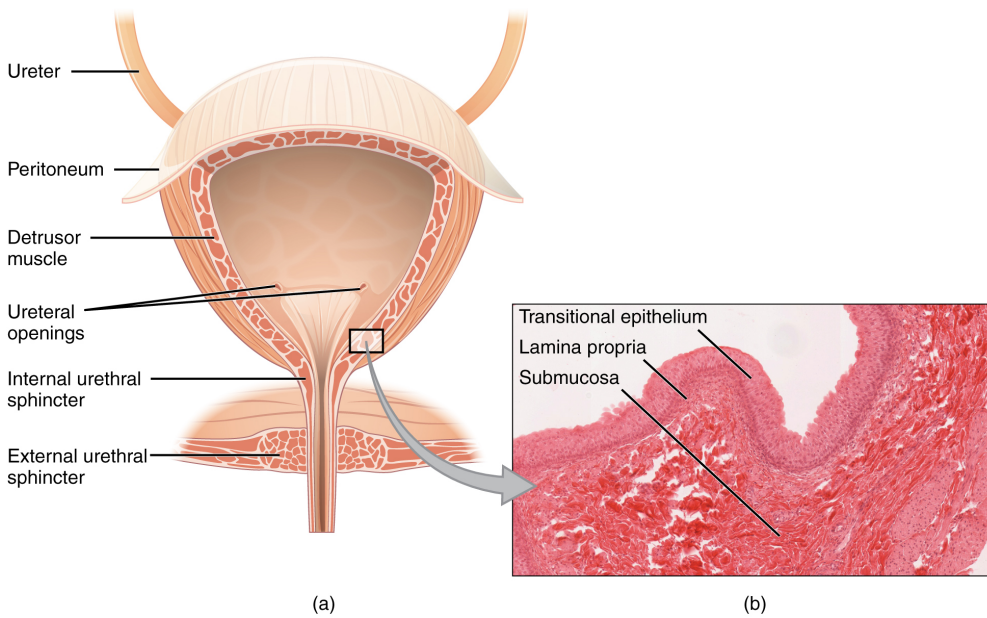
Male Urethra

The male urethra passes through the prostate gland immediately inferior to the bladder before passing below the pubic symphysis (see [\[link\]](#)**b**). The length of the male urethra varies between men but averages 20 cm in length. It is divided into four regions: the preprostatic urethra, the prostatic urethra, the membranous urethra, and the spongy or penile urethra. The preprostatic urethra is very short and incorporated into the bladder wall. The prostatic urethra passes through the prostate gland. During sexual intercourse, it receives sperm via the ejaculatory ducts and secretions from the seminal vesicles. Paired Cowper's glands (bulbourethral glands) produce and secrete mucus into the urethra to buffer urethral pH during sexual stimulation. The mucus neutralizes the usually acidic environment and lubricates the urethra, decreasing the resistance to ejaculation. The membranous urethra passes through the deep muscles of the perineum, where it is invested by the overlying urethral sphincters. The spongy urethra exits at the tip (external urethral orifice) of the penis after passing through the corpus spongiosum. Mucous glands are found along much of the length of the urethra and protect the urethra from extremes of urine pH. Innervation is the same in both males and females.

Bladder

The urinary bladder collects urine from both ureters ([\[link\]](#)). The bladder lies anterior to the uterus in females, posterior to the pubic bone and anterior to the rectum. During late pregnancy, its capacity is reduced due to compression by the enlarging uterus, resulting in increased frequency of urination. In males, the anatomy is similar, minus the uterus, and with the addition of the prostate inferior to the bladder. The bladder is partially **retroperitoneal** (outside the peritoneal cavity) with its peritoneal-covered "dome" projecting into the abdomen when the bladder is distended with urine.

Bladder



(a) Anterior cross section of the bladder. (b) The detrusor muscle of the bladder (source: monkey tissue) LM × 448. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Note:



View the [University of Michigan WebScope](#) to explore the tissue sample in greater detail.

The bladder is a highly distensible organ comprised of irregular crisscrossing bands of smooth muscle collectively called the **detrusor muscle**. The interior surface is made of transitional cellular epithelium that is structurally suited for the large volume fluctuations of the bladder. When empty, it resembles columnar epithelia, but when stretched, it “transitions” (hence the name) to a squamous appearance (see [\[link\]](#)). Volumes in adults can range from nearly zero to 500–600 mL.

The detrusor muscle contracts with significant force in the young. The bladder’s strength diminishes with age, but voluntary contractions of abdominal skeletal muscles can increase intra-abdominal pressure to promote more forceful bladder emptying. Such voluntary contraction is also used in forceful defecation and childbirth.

Micturition Reflex

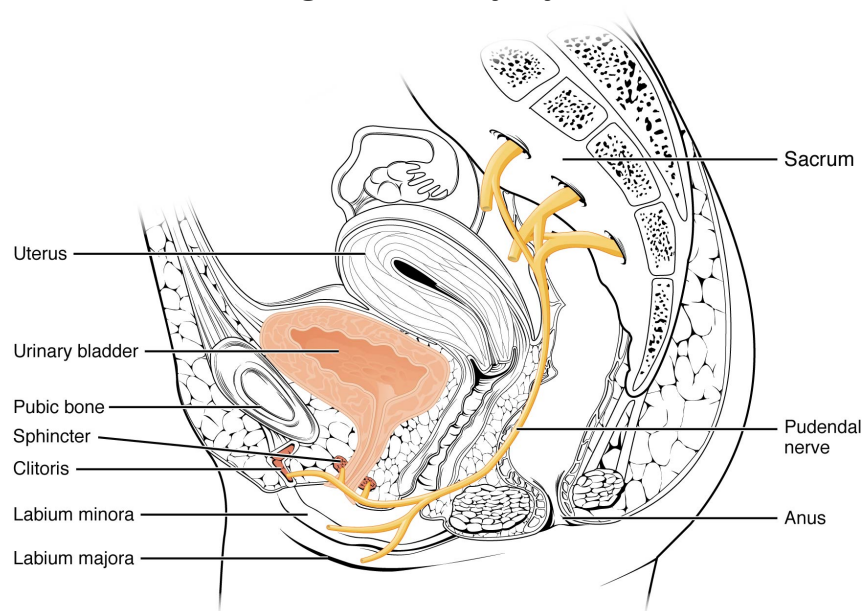
Micturition is a less-often used, but proper term for urination or voiding. It results from an interplay of involuntary and voluntary actions by the internal and external urethral sphincters. When bladder volume reaches about 150 mL, an urge to void is sensed but is easily overridden. Voluntary control of urination relies on consciously preventing relaxation of the external urethral sphincter to maintain urinary continence. As the bladder fills, subsequent urges become harder to ignore. Ultimately, voluntary constraint fails with resulting **incontinence**, which will occur as bladder volume approaches 300 to 400 mL.

Normal micturition is a result of stretch receptors in the bladder wall that transmit nerve impulses to the sacral region of the spinal cord to generate a spinal reflex. The resulting parasympathetic neural outflow causes contraction of the detrusor muscle and relaxation of the involuntary internal urethral sphincter. At the same time, the spinal cord inhibits somatic motor neurons, resulting in the relaxation of the skeletal muscle of the external urethral sphincter. The micturition reflex is active in infants but with maturity, children learn to override the reflex by asserting external sphincter control, thereby delaying voiding (potty training). This reflex may be preserved even in the face of spinal cord injury that results in paraplegia or

quadriplegia. However, relaxation of the external sphincter may not be possible in all cases, and therefore, periodic catheterization may be necessary for bladder emptying.

Nerves involved in the control of urination include the hypogastric, pelvic, and pudendal ([\[link\]](#)). Voluntary micturition requires an intact spinal cord and functional pudendal nerve arising from the **sacral micturition center**. Since the external urinary sphincter is voluntary skeletal muscle, actions by cholinergic neurons maintain contraction (and thereby continence) during filling of the bladder. At the same time, sympathetic nervous activity via the hypogastric nerves suppresses contraction of the detrusor muscle. With further bladder stretch, afferent signals traveling over sacral pelvic nerves activate parasympathetic neurons. This activates efferent neurons to release acetylcholine at the neuromuscular junctions, producing detrusor contraction and bladder emptying.

Nerves Innervating the Urinary System



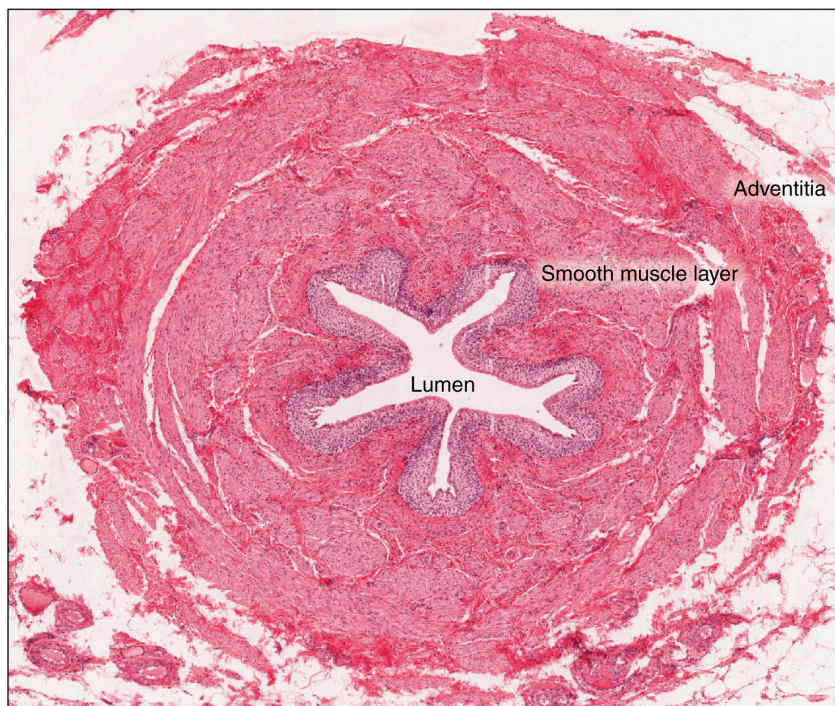
Ureters

The kidneys and ureters are completely retroperitoneal, and the bladder has a peritoneal covering only over the dome. As urine is formed, it drains into the calyces of the kidney, which merge to form the funnel-shaped renal pelvis in the hilum of each kidney. The renal pelvis narrows to become the

ureter of each kidney. As urine passes through the ureter, it does not passively drain into the bladder but rather is propelled by waves of peristalsis. As the ureters enter the pelvis, they sweep laterally, hugging the pelvic walls. As they approach the bladder, they turn medially and pierce the bladder wall obliquely. This is important because it creates an one-way valve (a **physiological sphincter** rather than an **anatomical sphincter**) that allows urine into the bladder but prevents reflux of urine from the bladder back into the ureter. Children born lacking this oblique course of the ureter through the bladder wall are susceptible to “vesicoureteral reflux,” which dramatically increases their risk of serious UTI. Pregnancy also increases the likelihood of reflux and UTI.

The ureters are approximately 30 cm long. The inner mucosa is lined with transitional epithelium ([\[link\]](#)) and scattered goblet cells that secrete protective mucus. The muscular layer of the ureter consists of longitudinal and circular smooth muscles that create the peristaltic contractions to move the urine into the bladder without the aid of gravity. Finally, a loose adventitial layer composed of collagen and fat anchors the ureters between the parietal peritoneum and the posterior abdominal wall.

Ureter



Peristaltic contractions help to move urine

through the lumen with contributions from fluid pressure and gravity. LM \times 128. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Chapter Review

The urethra is the only urinary structure that differs significantly between males and females. This is due to the dual role of the male urethra in transporting both urine and semen. The urethra arises from the trigone area at the base of the bladder. Urination is controlled by an involuntary internal sphincter of smooth muscle and a voluntary external sphincter of skeletal muscle. The shorter female urethra contributes to the higher incidence of bladder infections in females. The male urethra receives secretions from the prostate gland, Cowper's gland, and seminal vesicles as well as sperm. The bladder is largely retroperitoneal and can hold up to 500–600 mL urine. Micturition is the process of voiding the urine and involves both involuntary and voluntary actions. Voluntary control of micturition requires a mature and intact sacral micturition center. It also requires an intact spinal cord. Loss of control of micturition is called incontinence and results in voiding when the bladder contains about 250 mL urine. The ureters are retroperitoneal and lead from the renal pelvis of the kidney to the trigone area at the base of the bladder. A thick muscular wall consisting of longitudinal and circular smooth muscle helps move urine toward the bladder by way of peristaltic contractions.

Review Questions

Exercise:

Problem: Peristaltic contractions occur in the _____.

- a. urethra
- b. bladder

- c. ureters
 - d. urethra, bladder, and ureters
-

Solution:

C

Exercise:

Problem:

Somatic motor neurons must be _____ to relax the external urethral sphincter to allow urination.

- a. stimulated
 - b. inhibited
-

Solution:

B

Exercise:

Problem:

Which part of the urinary system is *not* completely retroperitoneal?

- a. kidneys
 - b. ureters
 - c. bladder
 - d. nephrons
-

Solution:

C

Critical Thinking Questions

Exercise:**Problem:**

Why are females more likely to contract bladder infections than males?

Solution:

The longer urethra of males means bacteria must travel farther to the bladder to cause an infection.

Exercise:

Problem: Describe how forceful urination is accomplished.

Solution:

Forceful urination is accomplished by contraction of abdominal muscles.

Glossary

anatomical sphincter

smooth or skeletal muscle surrounding the lumen of a vessel or hollow organ that can restrict flow when contracted

detrusor muscle

smooth muscle in the bladder wall; fibers run in all directions to reduce the size of the organ when emptying it of urine

external urinary sphincter

skeletal muscle; must be relaxed consciously to void urine

internal urinary sphincter

smooth muscle at the juncture of the bladder and urethra; relaxes as the bladder fills to allow urine into the urethra

incontinence

loss of ability to control micturition

micturition

also called urination or voiding

physiological sphincter

sphincter consisting of circular smooth muscle indistinguishable from adjacent muscle but possessing differential innervations, permitting its function as a sphincter; structurally weak

retroperitoneal

outside the peritoneal cavity; in the case of the kidney and ureters, between the parietal peritoneum and the abdominal wall

sacral micturition center

group of neurons in the sacral region of the spinal cord that controls urination; acts reflexively unless its action is modified by higher brain centers to allow voluntary urination

trigone

area at the base of the bladder marked by the two ureters in the posterior–lateral aspect and the urethral orifice in the anterior aspect oriented like points on a triangle

urethra

transports urine from the bladder to the outside environment

Gross Anatomy of the Kidney

By the end of this section, you will be able to:

- Describe the external structure of the kidney, including its location, support structures, and covering
- Identify the major internal divisions and structures of the kidney
- Identify the major blood vessels associated with the kidney and trace the path of blood through the kidney
- Compare and contrast the cortical and juxtamedullary nephrons
- Name structures found in the cortex and medulla
- Describe the physiological characteristics of the cortex and medulla

The kidneys lie on either side of the spine in the retroperitoneal space between the parietal peritoneum and the posterior abdominal wall, well protected by muscle, fat, and ribs. They are roughly the size of your fist, and the male kidney is typically a bit larger than the female kidney. The kidneys are well vascularized, receiving about 25 percent of the cardiac output at rest.

Note:

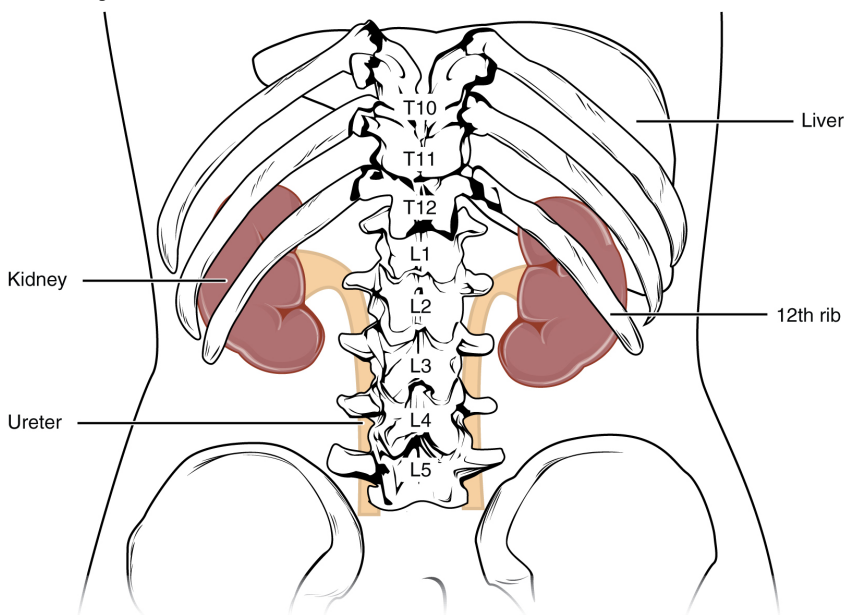


There have never been sufficient kidney donations to provide a kidney to each person needing one. Watch this [video](#) to learn about the TED (Technology, Entertainment, Design) Conference held in March 2011. In this video, Dr. Anthony Atala discusses a cutting-edge technique in which a new kidney is “printed.” The successful utilization of this technology is still several years in the future, but imagine a time when you can print a replacement organ or tissue on demand.

External Anatomy

The left kidney is located at about the T12 to L3 vertebrae, whereas the right is lower due to slight displacement by the liver. Upper portions of the kidneys are somewhat protected by the eleventh and twelfth ribs ([link](#)). Each kidney weighs about 125–175 g in males and 115–155 g in females. They are about 11–14 cm in length, 6 cm wide, and 4 cm thick, and are directly covered by a fibrous capsule composed of dense, irregular connective tissue that helps to hold their shape and protect them. This capsule is covered by a shock-absorbing layer of adipose tissue called the **renal fat pad**, which in turn is encompassed by a tough renal fascia. The fascia and, to a lesser extent, the overlying peritoneum serve to firmly anchor the kidneys to the posterior abdominal wall in a retroperitoneal position.

Kidneys



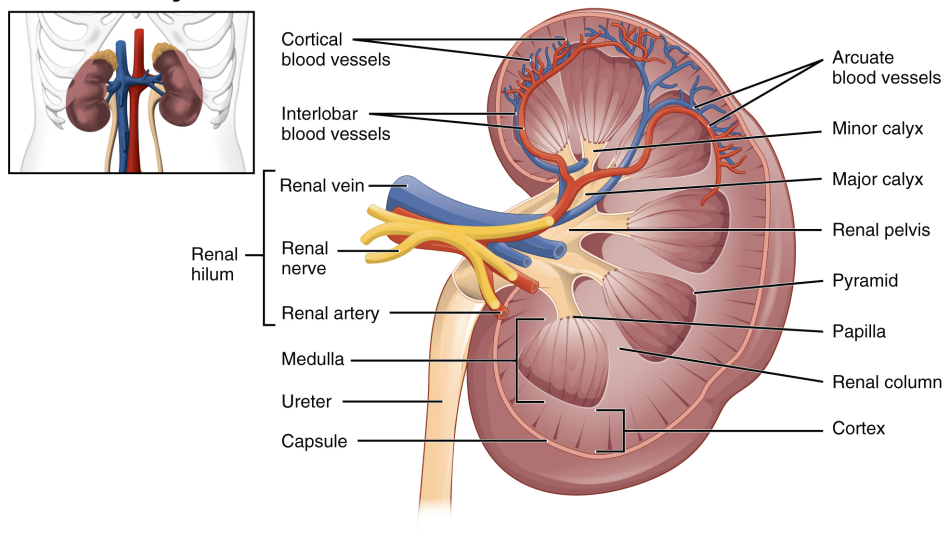
The kidneys are slightly protected by the ribs and are surrounded by fat for protection (not shown).

On the superior aspect of each kidney is the adrenal gland. The adrenal cortex directly influences renal function through the production of the hormone aldosterone to stimulate sodium reabsorption.

Internal Anatomy

A frontal section through the kidney reveals an outer region called the **renal cortex** and an inner region called the **medulla** ([\[link\]](#)). The **renal columns** are connective tissue extensions that radiate downward from the cortex through the medulla to separate the most characteristic features of the medulla, the **renal pyramids** and **renal papillae**. The papillae are bundles of collecting ducts that transport urine made by nephrons to the **calyces** of the kidney for excretion. The renal columns also serve to divide the kidney into 6–8 lobes and provide a supportive framework for vessels that enter and exit the cortex. The pyramids and renal columns taken together constitute the kidney lobes.

Left Kidney



Renal Hilum

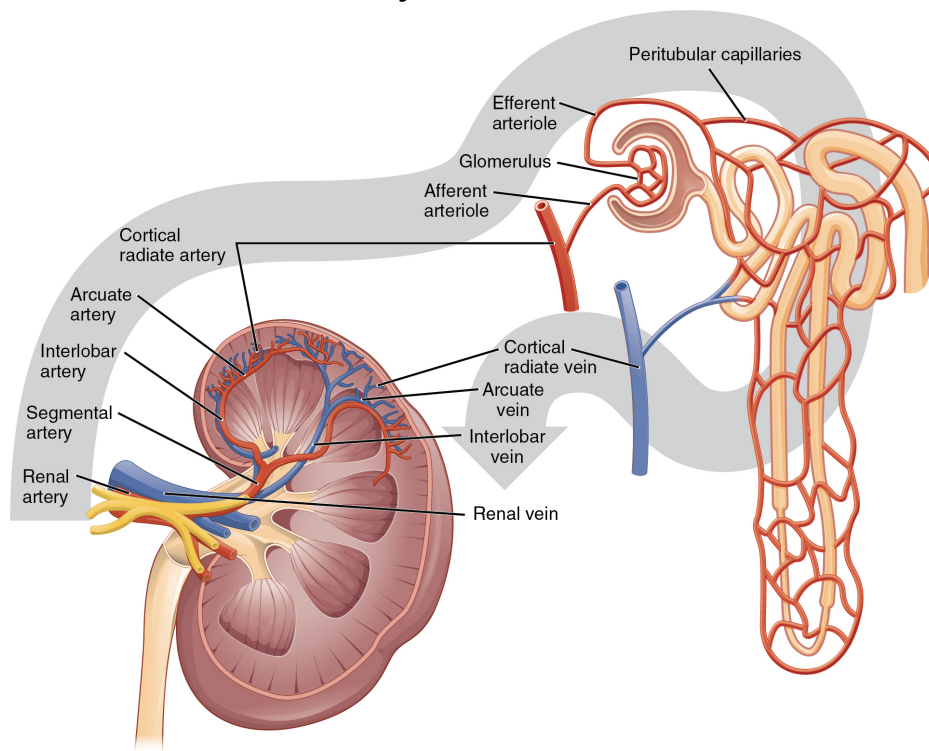
The **renal hilum** is the entry and exit site for structures servicing the kidneys: vessels, nerves, lymphatics, and ureters. The medial-facing hila are tucked into the sweeping convex outline of the cortex. Emerging from the hilum is the renal pelvis, which is formed from the major and minor calyces

in the kidney. The smooth muscle in the renal pelvis funnels urine via peristalsis into the ureter. The renal arteries form directly from the descending aorta, whereas the renal veins return cleansed blood directly to the inferior vena cava. The artery, vein, and renal pelvis are arranged in an anterior-to-posterior order.

Nephrons and Vessels

The renal artery first divides into segmental arteries, followed by further branching to form interlobar arteries that pass through the renal columns to reach the cortex ([link](#)). The interlobar arteries, in turn, branch into arcuate arteries, cortical radiate arteries, and then into afferent arterioles. The afferent arterioles service about 1.3 million nephrons in each kidney.

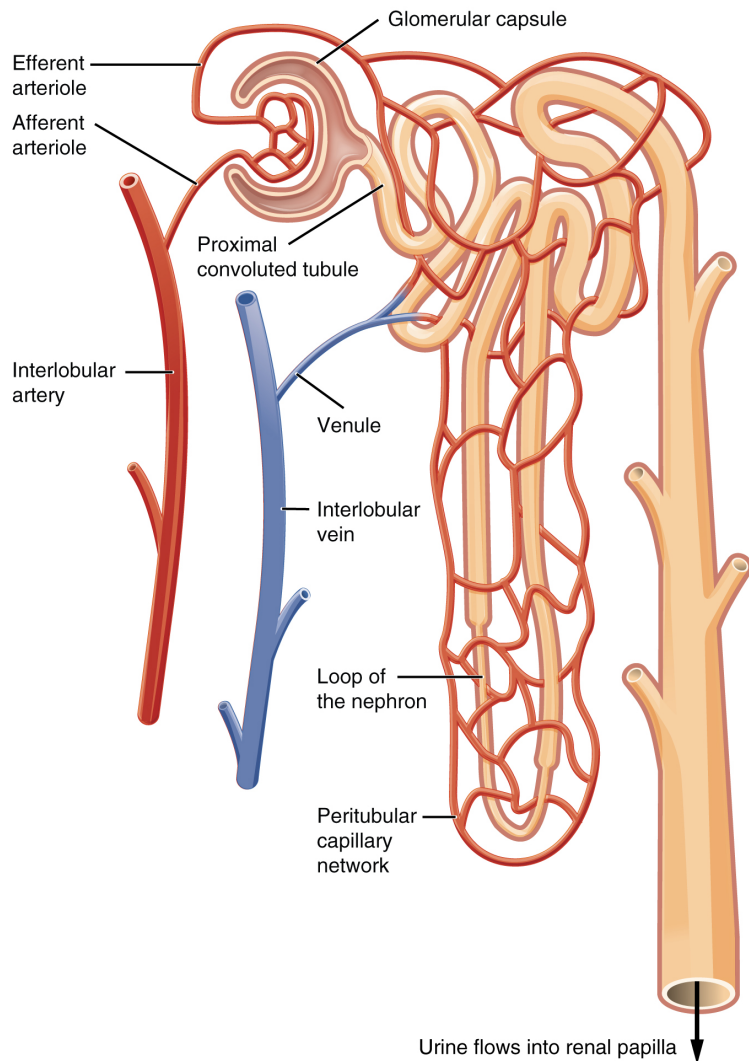
Blood Flow in the Kidney



Nephrons are the “functional units” of the kidney; they cleanse the blood and balance the constituents of the circulation. The afferent arterioles form a tuft of high-pressure capillaries about 200 μm in diameter, the **glomerulus**. The rest of the nephron consists of a continuous sophisticated

tubule whose proximal end surrounds the glomerulus in an intimate embrace—this is **Bowman's capsule**. The glomerulus and Bowman's capsule together form the **renal corpuscle**. As mentioned earlier, these glomerular capillaries filter the blood based on particle size. After passing through the renal corpuscle, the capillaries form a second arteriole, the **efferent arteriole** ([\[link\]](#)). These will next form a capillary network around the more distal portions of the nephron tubule, the **peritubular capillaries** and **vasa recta**, before returning to the venous system. As the glomerular filtrate progresses through the nephron, these capillary networks recover most of the solutes and water, and return them to the circulation. Since a capillary bed (the glomerulus) drains into a vessel that in turn forms a second capillary bed, the definition of a portal system is met. This is the only portal system in which an arteriole is found between the first and second capillary beds. (Portal systems also link the hypothalamus to the anterior pituitary, and the blood vessels of the digestive viscera to the liver.)

Blood Flow in the Nephron



The two capillary beds are clearly shown in this figure. The efferent arteriole is the connecting vessel between the glomerulus and the peritubular capillaries and vasa recta.

Note:



Visit this [link](#) to view an interactive tutorial of the flow of blood through the kidney.

Cortex

In a dissected kidney, it is easy to identify the cortex; it appears lighter in color compared to the rest of the kidney. All of the renal corpuscles as well as both the **proximal convoluted tubules (PCTs)** and **distal convoluted tubules** are found here. Some nephrons have a short **loop of Henle** that does not dip beyond the cortex. These nephrons are called **cortical nephrons**. About 15 percent of nephrons have long loops of Henle that extend deep into the medulla and are called **juxtamedullary nephrons**.

Chapter Review

As noted previously, the structure of the kidney is divided into two principle regions—the peripheral rim of cortex and the central medulla. The two kidneys receive about 25 percent of cardiac output. They are protected in the retroperitoneal space by the renal fat pad and overlying ribs and muscle. Ureters, blood vessels, lymph vessels, and nerves enter and leave at the renal hilum. The renal arteries arise directly from the aorta, and the renal veins drain directly into the inferior vena cava. Kidney function is derived from the actions of about 1.3 million nephrons per kidney; these are the “functional units.” A capillary bed, the glomerulus, filters blood and the filtrate is captured by Bowman’s capsule. A portal system is formed when the blood flows through a second capillary bed surrounding the proximal and distal convoluted tubules and the loop of Henle. Most water and solutes are recovered by this second capillary bed. This filtrate is processed and finally gathered by collecting ducts that drain into the minor calyces, which

merge to form major calyces; the filtrate then proceeds to the renal pelvis and finally the ureters.

Review Questions

Exercise:

Problem:

The renal pyramids are separated from each other by extensions of the renal cortex called _____.

- a. renal medulla
- b. minor calyces
- c. medullary cortices
- d. renal columns

Solution:

D

Exercise:

Problem:

The primary structure found within the medulla is the _____.

- a. loop of Henle
- b. minor calyces
- c. portal system
- d. ureter

Solution:

A

Exercise:

Problem: The right kidney is slightly lower because _____.

- a. it is displaced by the liver
- b. it is displaced by the heart
- c. it is slightly smaller
- d. it needs protection of the lower ribs

Solution:

A

Critical Thinking Questions

Exercise:

Problem: What anatomical structures provide protection to the kidney?

Solution:

Retroperitoneal anchoring, renal fat pads, and ribs provide protection to the kidney.

Exercise:

Problem:

How does the renal portal system differ from the hypothalamo–hypophyseal and digestive portal systems?

Solution:

The renal portal system has an artery between the first and second capillary bed. The others have a vein.

Exercise:

Problem: Name the structures found in the renal hilum.

Solution:

The structures found in the renal hilum are arteries, veins, ureters, lymphatics, and nerves.

Glossary

Bowman's capsule

cup-shaped sack lined by a simple squamous epithelium (parietal surface) and specialized cells called podocytes (visceral surface) that participate in the filtration process; receives the filtrate which then passes on to the PCTs

calyces

cup-like structures receiving urine from the collecting ducts where it passes on to the renal pelvis and ureter

cortical nephrons

nephrons with loops of Henle that do not extend into the renal medulla

distal convoluted tubules

portions of the nephron distal to the loop of Henle that receive hyposmotic filtrate from the loop of Henle and empty into collecting ducts

efferent arteriole

arteriole carrying blood from the glomerulus to the capillary beds around the convoluted tubules and loop of Henle; portion of the portal system

glomerulus

tuft of capillaries surrounded by Bowman's capsule; filters the blood based on size

juxtamedullary nephrons

nephrons adjacent to the border of the cortex and medulla with loops of Henle that extend into the renal medulla

loop of Henle

descending and ascending portions between the proximal and distal convoluted tubules; those of cortical nephrons do not extend into the medulla, whereas those of juxtamedullary nephrons do extend into the medulla

nephrons

functional units of the kidney that carry out all filtration and modification to produce urine; consist of renal corpuscles, proximal and distal convoluted tubules, and descending and ascending loops of Henle; drain into collecting ducts

medulla

inner region of kidney containing the renal pyramids

peritubular capillaries

second capillary bed of the renal portal system; surround the proximal and distal convoluted tubules; associated with the vasa recta

proximal convoluted tubules (PCTs)

tortuous tubules receiving filtrate from Bowman's capsule; most active part of the nephron in reabsorption and secretion

renal columns

extensions of the renal cortex into the renal medulla; separates the renal pyramids; contains blood vessels and connective tissues

renal corpuscle

consists of the glomerulus and Bowman's capsule

renal cortex

outer part of kidney containing all of the nephrons; some nephrons have loops of Henle extending into the medulla

renal fat pad

adipose tissue between the renal fascia and the renal capsule that provides protective cushioning to the kidney

renal hilum

recessed medial area of the kidney through which the renal artery, renal vein, ureters, lymphatics, and nerves pass

renal papillae

medullary area of the renal pyramids where collecting ducts empty urine into the minor calyces

renal pyramids

six to eight cone-shaped tissues in the medulla of the kidney containing collecting ducts and the loops of Henle of juxtamedullary nephrons

vasa recta

branches of the efferent arterioles that parallel the course of the loops of Henle and are continuous with the peritubular capillaries; with the glomerulus, form a portal system

Microscopic Anatomy of the Kidney

By the end of this section, you will be able to:

- Distinguish the histological differences between the renal cortex and medulla
- Describe the structure of the filtration membrane
- Identify the major structures and subdivisions of the renal corpuscles, renal tubules, and renal capillaries
- Discuss the function of the peritubular capillaries and vasa recta
- Identify the location of the juxtaglomerular apparatus and describe the cells that line it
- Describe the histology of the proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting ducts

The renal structures that conduct the essential work of the kidney cannot be seen by the naked eye. Only a light or electron microscope can reveal these structures. Even then, serial sections and computer reconstruction are necessary to give us a comprehensive view of the functional anatomy of the nephron and its associated blood vessels.

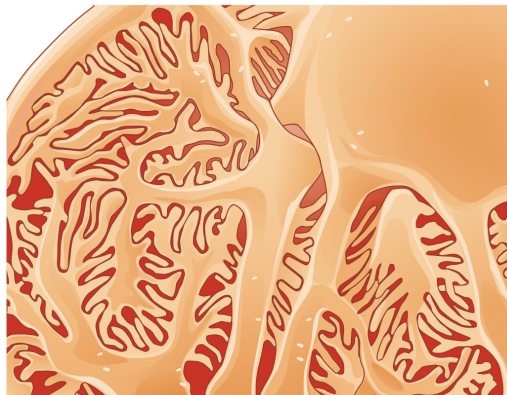
Nephrons: The Functional Unit

Nephrons take a simple filtrate of the blood and modify it into urine. Many changes take place in the different parts of the nephron before urine is created for disposal. The term **forming urine** will be used hereafter to describe the filtrate as it is modified into true urine. The principle task of the nephron population is to balance the plasma to homeostatic set points and excrete potential toxins in the urine. They do this by accomplishing three principle functions—filtration, reabsorption, and secretion. They also have additional secondary functions that exert control in three areas: blood pressure (via production of **renin**), red blood cell production (via the hormone EPO), and calcium absorption (via conversion of calcidiol into calcitriol, the active form of vitamin D).

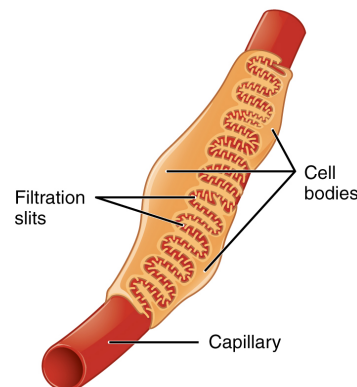
Renal Corpuscle

As discussed earlier, the renal corpuscle consists of a tuft of capillaries called the glomerulus that is largely surrounded by Bowman's (glomerular) capsule. The glomerulus is a high-pressure capillary bed between afferent and efferent arterioles. Bowman's capsule surrounds the glomerulus to form a lumen, and captures and directs this filtrate to the PCT. The outermost part of Bowman's capsule, the parietal layer, is a simple squamous epithelium. It transitions onto the glomerular capillaries in an intimate embrace to form the visceral layer of the capsule. Here, the cells are not squamous, but uniquely shaped cells (**podocytes**) extending finger-like arms (**pedicels**) to cover the glomerular capillaries ([\[link\]](#)). These projections interdigitate to form **filtration slits**, leaving small gaps between the digits to form a sieve. As blood passes through the glomerulus, 10 to 20 percent of the plasma filters between these sieve-like fingers to be captured by Bowman's capsule and funneled to the PCT. Where the fenestrae (windows) in the glomerular capillaries match the spaces between the podocyte "fingers," the only thing separating the capillary lumen and the lumen of Bowman's capsule is their shared basement membrane ([\[link\]](#)). These three features comprise what is known as the filtration membrane. This membrane permits very rapid movement of filtrate from capillary to capsule through pores that are only 70 nm in diameter.

Podocytes



(a)

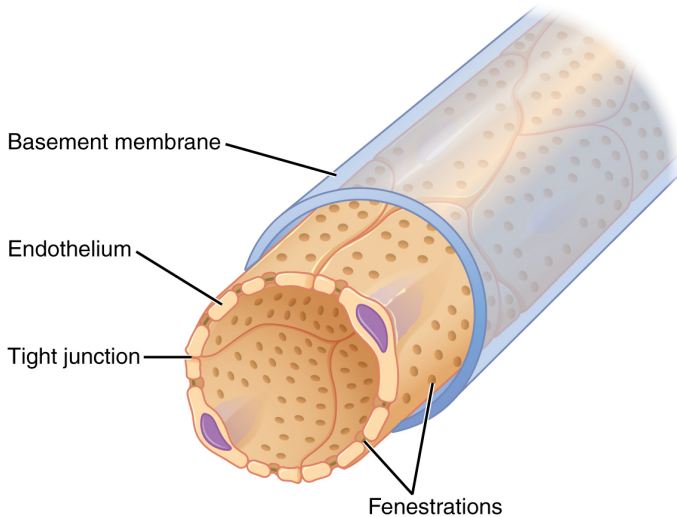


(b)

Podocytes interdigitate with structures called pedicels and filter substances in a way similar to fenestrations. In (a), the large cell body can be seen at the top right corner, with branches extending from the cell body. The smallest finger-like extensions are the pedicels.

Pedicels on one podocyte always interdigitate with the pedicels of another podocyte. (b) This capillary has three podocytes wrapped around it.

Fenestrated Capillary



Fenestrations allow many substances to diffuse from the blood based primarily on size.

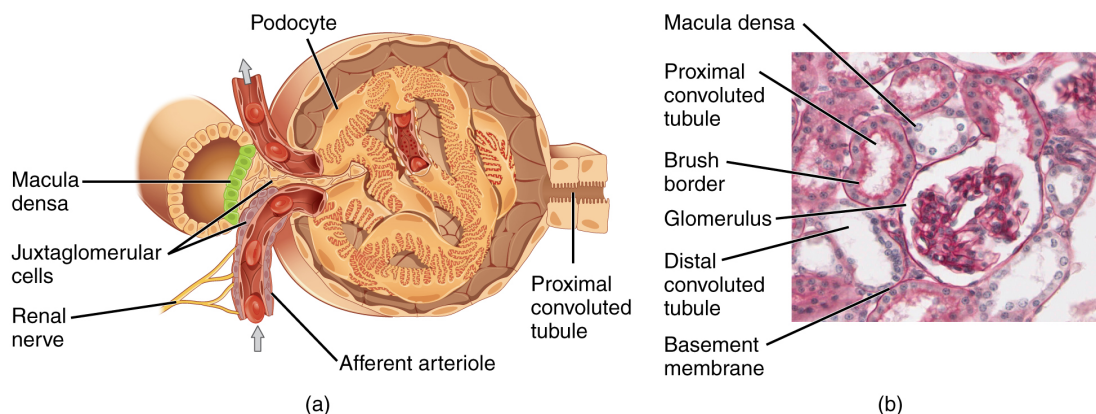
The **fenestrations** prevent filtration of blood cells or large proteins, but allow most other constituents through. These substances cross readily if they are less than 4 nm in size and most pass freely up to 8 nm in size. An additional factor affecting the ability of substances to cross this barrier is their electric charge. The proteins associated with these pores are negatively charged, so they tend to repel negatively charged substances and allow positively charged substances to pass more readily. The basement membrane prevents filtration of medium-to-large proteins such as globulins. There are also **mesangial** cells in the filtration membrane that can contract to help regulate the rate of filtration of the glomerulus. Overall, filtration is regulated by fenestrations in capillary endothelial cells, podocytes with filtration slits, membrane charge, and the basement membrane between

capillary cells. The result is the creation of a filtrate that does not contain cells or large proteins, and has a slight predominance of positively charged substances.

Lying just outside Bowman's capsule and the glomerulus is the **juxtaglomerular apparatus (JGA)** ([link](#)). At the juncture where the afferent and efferent arterioles enter and leave Bowman's capsule, the initial part of the distal convoluted tubule (DCT) comes into direct contact with the arterioles. The wall of the DCT at that point forms a part of the JGA known as the **macula densa**. This cluster of cuboidal epithelial cells monitors the fluid composition of fluid flowing through the DCT. In response to the concentration of Na^+ in the fluid flowing past them, these cells release paracrine signals. They also have a single, nonmotile cilium that responds to the rate of fluid movement in the tubule. The paracrine signals released in response to changes in flow rate and Na^+ concentration are adenosine triphosphate (ATP) and adenosine.

Juxtaglomerular Apparatus and Glomerulus

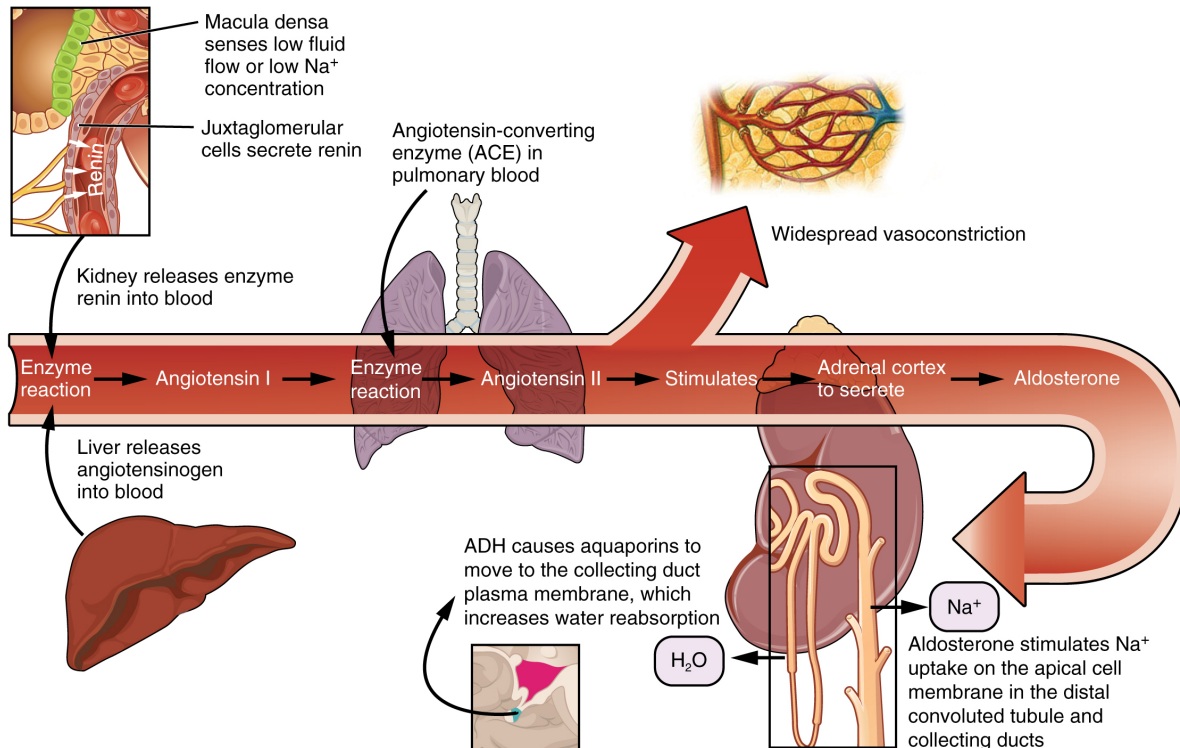
(a) The JGA allows specialized cells to monitor the composition of the fluid in the DCT and adjust the glomerular filtration rate. (b) This micrograph shows the glomerulus and surrounding structures. LM $\times 1540$. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



A second cell type in this apparatus is the **juxtaglomerular cell**. This is a modified, smooth muscle cell lining the afferent arteriole that can contract or relax in response to ATP or adenosine released by the macula densa. Such contraction and relaxation regulate blood flow to the glomerulus. If

the osmolarity of the filtrate is too high (hyperosmotic), the juxtaglomerular cells will contract, decreasing the glomerular filtration rate (GFR) so less plasma is filtered, leading to less urine formation and greater retention of fluid. This will ultimately decrease blood osmolarity toward the physiologic norm. If the osmolarity of the filtrate is too low, the juxtaglomerular cells will relax, increasing the GFR and enhancing the loss of water to the urine, causing blood osmolarity to rise. In other words, when osmolarity goes up, filtration and urine formation decrease and water is retained. When osmolarity goes down, filtration and urine formation increase and water is lost by way of the urine. The net result of these opposing actions is to keep the rate of filtration relatively constant. A second function of the macula densa cells is to regulate renin release from the juxtaglomerular cells of the afferent arteriole ([\[link\]](#)). Active renin is a protein comprised of 304 amino acids that cleaves several amino acids from **angiotensinogen** to produce **angiotensin I**. Angiotensin I is not biologically active until converted to angiotensin II by **angiotensin-converting enzyme (ACE)** from the lungs. **Angiotensin II** is a systemic vasoconstrictor that helps to regulate blood pressure by increasing it. Angiotensin II also stimulates the release of the steroid hormone aldosterone from the adrenal cortex. Aldosterone stimulates Na^+ reabsorption by the kidney, which also results in water retention and increased blood pressure.

Conversion of Angiotensin I to Angiotensin II



The enzyme renin converts the pro-enzyme angiotensin I; the lung-derived enzyme ACE converts angiotensin I into active angiotensin II.

Proximal Convoluted Tubule (PCT)

Filtered fluid collected by Bowman's capsule enters into the PCT. It is called convoluted due to its tortuous path. Simple cuboidal cells form this tubule with prominent microvilli on the luminal surface, forming a **brush border**. These microvilli create a large surface area to maximize the absorption and secretion of solutes (Na^+ , Cl^- , glucose, etc.), the most essential function of this portion of the nephron. These cells actively transport ions across their membranes, so they possess a high concentration of mitochondria in order to produce sufficient ATP.

Loop of Henle

The descending and ascending portions of the loop of Henle (sometimes referred to as the nephron loop) are, of course, just continuations of the same tubule. They run adjacent and parallel to each other after having made a hairpin turn at the deepest point of their descent. The descending loop of Henle consists of an initial short, thick portion and long, thin portion, whereas the ascending loop consists of an initial short, thin portion followed by a long, thick portion. The descending thick portion consists of simple cuboidal epithelium similar to that of the PCT. The descending and ascending thin portions consist of simple squamous epithelium. As you will see later, these are important differences, since different portions of the loop have different permeabilities for solutes and water. The ascending thick portion consists of simple cuboidal epithelium similar to the DCT.

Distal Convoluted Tubule (DCT)

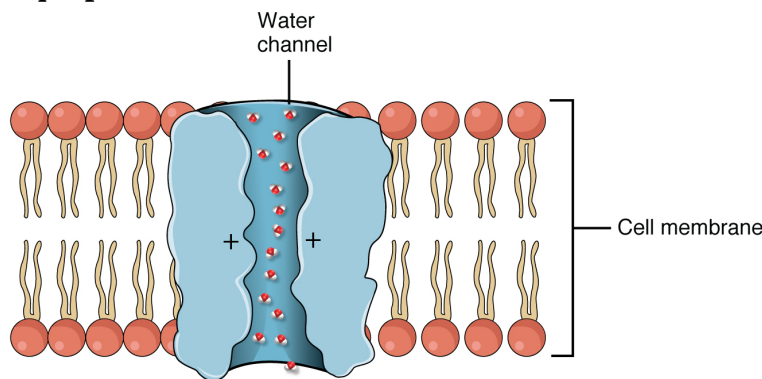
The DCT, like the PCT, is very tortuous and formed by simple cuboidal epithelium, but it is shorter than the PCT. These cells are not as active as those in the PCT; thus, there are fewer microvilli on the apical surface. However, these cells must also pump ions against their concentration gradient, so you will find a large number of mitochondria, although fewer than in the PCT.

Collecting Ducts

The collecting ducts are continuous with the nephron but not technically part of it. In fact, each duct collects filtrate from several nephrons for final modification. Collecting ducts merge as they descend deeper in the medulla to form about 30 terminal ducts, which empty at a papilla. They are lined with simple squamous epithelium with receptors for ADH. When stimulated by ADH, these cells will insert **aquaporin** channel proteins into their membranes, which as their name suggests, allow water to pass from the duct lumen through the cells and into the interstitial spaces to be

recovered by the vasa recta. This process allows for the recovery of large amounts of water from the filtrate back into the blood. In the absence of ADH, these channels are not inserted, resulting in the excretion of water in the form of dilute urine. Most, if not all, cells of the body contain aquaporin molecules, whose channels are so small that only water can pass. At least 10 types of aquaporins are known in humans, and six of those are found in the kidney. The function of all aquaporins is to allow the movement of water across the lipid-rich, hydrophobic cell membrane ([\[link\]](#)).

Aquaporin Water Channel



Positive charges inside the channel prevent the leakage of electrolytes across the cell membrane, while allowing water to move due to osmosis.

Chapter Review

The functional unit of the kidney, the nephron, consists of the renal corpuscle, PCT, loop of Henle, and DCT. Cortical nephrons have short loops of Henle, whereas juxtamedullary nephrons have long loops of Henle extending into the medulla. About 15 percent of nephrons are juxtamedullary. The glomerulus is a capillary bed that filters blood principally based on particle size. The filtrate is captured by Bowman's capsule and directed to the PCT. A filtration membrane is formed by the fused basement membranes of the podocytes and the capillary endothelial cells that they embrace. Contractile mesangial cells further perform a role in

regulating the rate at which the blood is filtered. Specialized cells in the JGA produce paracrine signals to regulate blood flow and filtration rates of the glomerulus. Other JGA cells produce the enzyme renin, which plays a central role in blood pressure regulation. The filtrate enters the PCT where absorption and secretion of several substances occur. The descending and ascending limbs of the loop of Henle consist of thick and thin segments. Absorption and secretion continue in the DCT but to a lesser extent than in the PCT. Each collecting duct collects forming urine from several nephrons and responds to the posterior pituitary hormone ADH by inserting aquaporin water channels into the cell membrane to fine tune water recovery.

Review Questions

Exercise:

Problem: Blood filtrate is captured in the lumen of the _____.

- a. glomerulus
- b. Bowman's capsule
- c. calyces
- d. renal papillae

Solution:

B

Exercise:

Problem:

What are the names of the capillaries following the efferent arteriole?

- a. arcuate and medullary
- b. interlobar and interlobular
- c. peritubular and vasa recta
- d. peritubular and medullary

Solution:

C

Exercise:

Problem: The functional unit of the kidney is called _____.

- a. the renal hilus
- b. the renal corpuscle
- c. the nephron
- d. Bowman's capsule

Solution:

C

Critical Thinking Questions

Exercise:

Problem: Which structures make up the renal corpuscle?

Solution:

The structures that make up the renal corpuscle are the glomerulus, Bowman's capsule, and PCT.

Exercise:

Problem:

What are the major structures comprising the filtration membrane?

Solution:

The major structures comprising the filtration membrane are fenestrations and podocyte fenestra, fused basement membrane, and filtration slits.

Glossary

angiotensin-converting enzyme (ACE)

enzyme produced by the lungs that catalyzes the reaction of inactive angiotensin I into active angiotensin II

angiotensin I

protein produced by the enzymatic action of renin on angiotensinogen; inactive precursor of angiotensin II

angiotensin II

protein produced by the enzymatic action of ACE on inactive angiotensin I; actively causes vasoconstriction and stimulates aldosterone release by the adrenal cortex

angiotensinogen

inactive protein in the circulation produced by the liver; precursor of angiotensin I; must be modified by the enzymes renin and ACE to be activated

aquaporin

protein-forming water channels through the lipid bilayer of the cell; allows water to cross; activation in the collecting ducts is under the control of ADH

brush border

formed by microvilli on the surface of certain cuboidal cells; in the kidney it is found in the PCT; increases surface area for absorption in the kidney

fenestrations

small windows through a cell, allowing rapid filtration based on size; formed in such a way as to allow substances to cross through a cell

without mixing with cell contents

filtration slits

formed by pedicels of podocytes; substances filter between the pedicels based on size

forming urine

filtrate undergoing modifications through secretion and reabsorption before true urine is produced

juxtaglomerular apparatus (JGA)

located at the juncture of the DCT and the afferent and efferent arterioles of the glomerulus; plays a role in the regulation of renal blood flow and GFR

juxtaglomerular cell

modified smooth muscle cells of the afferent arteriole; secretes renin in response to a drop in blood pressure

macula densa

cells found in the part of the DCT forming the JGA; sense Na^+ concentration in the forming urine

mesangial

contractile cells found in the glomerulus; can contract or relax to regulate filtration rate

pedicels

finger-like projections of podocytes surrounding glomerular capillaries; interdigitate to form a filtration membrane

podocytes

cells forming finger-like processes; form the visceral layer of Bowman's capsule; pedicels of the podocytes interdigitate to form a filtration membrane

renin

enzyme produced by juxtaglomerular cells in response to decreased blood pressure or sympathetic nervous activity; catalyzes the conversion of angiotensinogen into angiotensin I

Physiology of Urine Formation

By the end of this section, you will be able to:

- Describe the hydrostatic and colloid osmotic forces that favor and oppose filtration
- Describe glomerular filtration rate (GFR), state the average value of GFR, and explain how clearance rate can be used to measure GFR
- Predict specific factors that will increase or decrease GFR
- State the percent of the filtrate that is normally reabsorbed and explain why the process of reabsorption is so important
- Calculate daily urine production
- List common symptoms of kidney failure

Having reviewed the anatomy and microanatomy of the urinary system, now is the time to focus on the physiology. You will discover that different parts of the nephron utilize specific processes to produce urine: filtration, reabsorption, and secretion. You will learn how each of these processes works and where they occur along the nephron and collecting ducts. The physiologic goal is to modify the composition of the plasma and, in doing so, produce the waste product urine.

Failure of the renal anatomy and/or physiology can lead suddenly or gradually to renal failure. In this event, a number of symptoms, signs, or laboratory findings point to the diagnosis ([\[link\]](#)).

| Symptoms of Kidney Failure |
|----------------------------|
| Weakness |
| Lethargy |
| Shortness of breath |

| Symptoms of Kidney Failure |
|---------------------------------------|
| Widespread edema |
| Anemia |
| Metabolic acidosis |
| Metabolic alkalosis |
| Heart arrhythmias |
| Uremia (high urea level in the blood) |
| Loss of appetite |
| Fatigue |
| Excessive urination |
| Oliguria (too little urine output) |

Glomerular Filtration Rate (GFR)

The volume of filtrate formed by both kidneys per minute is termed the **glomerular filtration rate (GFR)**. The heart pumps about 5 L blood per min under resting conditions. Approximately 20 percent or one liter enters the kidneys to be filtered. On average, this liter results in the production of about 125 mL/min filtrate produced in men (range of 90 to 140 mL/min) and 105 mL/min filtrate produced in women (range of 80 to 125 mL/min). This amount equates to a volume of about 180 L/day in men and 150 L/day in women. Ninety-nine percent of this filtrate is returned to the circulation by reabsorption so that only about 1–2 liters of urine are produced per day ([link](#)).

Calculating Urine Formation per Day

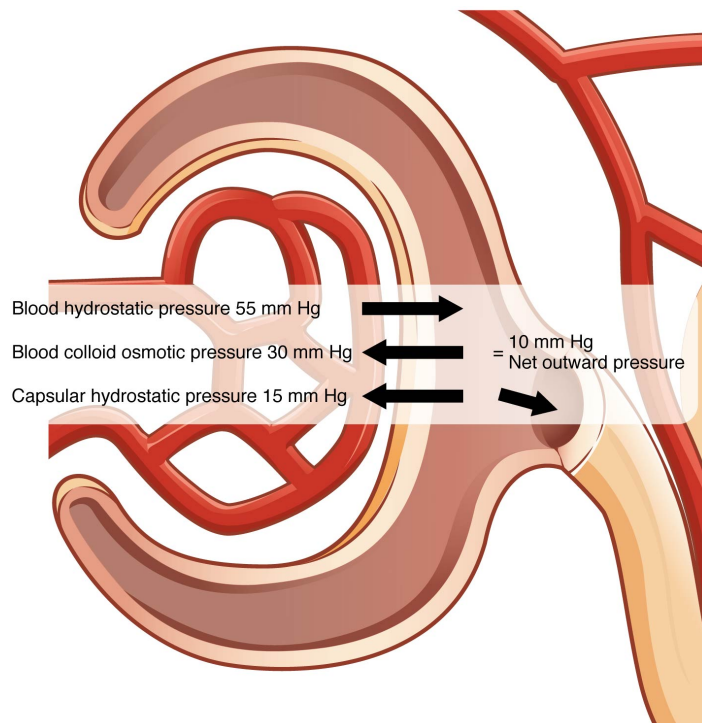
| | Flow per minute (mL) | Calculation |
|----------------------------------|---|---|
| Renal blood flow | 1050 | <p>Cardiac output is about 5000 mL/minute, of which 21 percent flows through the kidney.</p> $5000 \times 0.21 = 1050 \text{ mL blood/min}$ |
| Renal plasma flow | 578 | <p>Renal plasma flow equals the blood flow per minute times the hematocrit. If a person has a hematocrit of 45, then the renal plasma flow is 55 percent.</p> $1050 \times 0.55 = 578 \text{ mL plasma/min}$ |
| Glomerular filtration rate | 110 | <p>The GFR is the amount of plasma entering Bowman's capsule per minute. It is the renal plasma flow times the fraction that enters the renal capsule (19 percent).</p> $578 \times 0.19 = 110 \text{ mL filtrate/min}$ |

| Calculating Urine Formation per Day | | |
|-------------------------------------|-------------------------------|---|
| | Flow per minute (mL) | Calculation |
| Urine | 1296 ml/day | <p>The filtrate not recovered by the kidney is the urine that will be eliminated. It is the GFR times the fraction of the filtrate that is not reabsorbed (0.8 percent).</p> <p>$110 \times .008 = 0.9 \text{ mL urine /min}$</p> <p>Multiply urine/min times 60 minutes times 24 hours to get daily urine production.</p> <p>$0.9 \times 60 \times 24 = 1296 \text{ mL/day urine}$</p> |

GFR is influenced by the hydrostatic pressure and colloid osmotic pressure on either side of the capillary membrane of the glomerulus. Recall that filtration occurs as pressure forces fluid and solutes through a semipermeable barrier with the solute movement constrained by particle size. Hydrostatic pressure is the pressure produced by a fluid against a surface. If you have a fluid on both sides of a barrier, both fluids exert a pressure in opposing directions. Net fluid movement will be in the direction of the lower pressure. Osmosis is the movement of solvent (water) across a membrane that is impermeable to a solute in the solution. This creates a pressure, osmotic pressure, which will exist until the solute concentration is the same on both sides of a semipermeable membrane. As long as the concentration differs, water will move. Glomerular filtration occurs when glomerular hydrostatic pressure exceeds the luminal hydrostatic pressure of Bowman's capsule. There is also an opposing force, the osmotic pressure, which is typically higher in the glomerular capillary.

To understand why this is so, look more closely at the microenvironment on either side of the filtration membrane. You will find osmotic pressure exerted by the solutes inside the lumen of the capillary as well as inside of Bowman's capsule. Since the filtration membrane limits the size of particles crossing the membrane, the osmotic pressure inside the glomerular capillary is higher than the osmotic pressure in Bowman's capsule. Recall that cells and the medium-to-large proteins cannot pass between the podocyte processes or through the fenestrations of the capillary endothelial cells. This means that red and white blood cells, platelets, albumins, and other proteins too large to pass through the filter remain in the capillary, creating an average colloid osmotic pressure of 30 mm Hg within the capillary. The absence of proteins in Bowman's space (the lumen within Bowman's capsule) results in an osmotic pressure near zero. Thus, the only pressure moving fluid across the capillary wall into the lumen of Bowman's space is hydrostatic pressure. Hydrostatic (fluid) pressure is sufficient to push water through the membrane despite the osmotic pressure working against it. The sum of all of the influences, both osmotic and hydrostatic, results in a **net filtration pressure (NFP)** of about 10 mm Hg ([\[link\]](#)).

Net Filtration Pressure



The NFP is the sum of osmotic and

hydrostatic pressures.

A proper concentration of solutes in the blood is important in maintaining osmotic pressure both in the glomerulus and systemically. There are disorders in which too much protein passes through the filtration slits into the kidney filtrate. This excess protein in the filtrate leads to a deficiency of circulating plasma proteins. In turn, the presence of protein in the urine increases its osmolarity; this holds more water in the filtrate and results in an increase in urine volume. Because there is less circulating protein, principally albumin, the osmotic pressure of the blood falls. Less osmotic pressure pulling water into the capillaries tips the balance towards hydrostatic pressure, which tends to push it out of the capillaries. The net effect is that water is lost from the circulation to interstitial tissues and cells. This “plumps up” the tissues and cells, a condition termed **systemic edema**.

Net Filtration Pressure (NFP)

NFP determines filtration rates through the kidney. It is determined as follows:

$$\text{NFP} = \text{Glomerular blood hydrostatic pressure (GBHP)} - [\text{capsular hydrostatic pressure (CHP)} + \text{blood colloid osmotic pressure (BCOP)}] = 10 \text{ mm Hg}$$

That is:

$$\text{NFP} = \text{GBHP} - [\text{CHP} + \text{BCOP}] = 10 \text{ mm Hg}$$

Or:

$$\text{NFP} = 55 - [15 + 30] = 10 \text{ mm Hg}$$

As you can see, there is a low net pressure across the filtration membrane. Intuitively, you should realize that minor changes in osmolarity of the blood or changes in capillary blood pressure result in major changes in the amount

of filtrate formed at any given point in time. The kidney is able to cope with a wide range of blood pressures. In large part, this is due to the autoregulatory nature of smooth muscle. When you stretch it, it contracts. Thus, when blood pressure goes up, smooth muscle in the afferent capillaries contracts to limit any increase in blood flow and filtration rate. When blood pressure drops, the same capillaries relax to maintain blood flow and filtration rate. The net result is a relatively steady flow of blood into the glomerulus and a relatively steady filtration rate in spite of significant systemic blood pressure changes. Mean arterial blood pressure is calculated by adding $\frac{1}{3}$ of the difference between the systolic and diastolic pressures to the diastolic pressure. Therefore, if the blood pressure is 110/80, the difference between systolic and diastolic pressure is 30. One third of this is 10, and when you add this to the diastolic pressure of 80, you arrive at a calculated mean arterial pressure of 90 mm Hg. Therefore, if you use mean arterial pressure for the GBHP in the formula for calculating NFP, you can determine that as long as mean arterial pressure is above approximately 60 mm Hg, the pressure will be adequate to maintain glomerular filtration. Blood pressures below this level will impair renal function and cause systemic disorders that are severe enough to threaten survival. This condition is called shock.

Determination of the GFR is one of the tools used to assess the kidney's excretory function. This is more than just an academic exercise. Since many drugs are excreted in the urine, a decline in renal function can lead to toxic accumulations. Additionally, administration of appropriate drug dosages for those drugs primarily excreted by the kidney requires an accurate assessment of GFR. GFR can be estimated closely by intravenous administration of **inulin**. Inulin is a plant polysaccharide that is neither reabsorbed nor secreted by the kidney. Its appearance in the urine is directly proportional to the rate at which it is filtered by the renal corpuscle. However, since measuring inulin clearance is cumbersome in the clinical setting, most often, the GFR is estimated by measuring naturally occurring creatinine, a protein-derived molecule produced by muscle metabolism that is not reabsorbed and only slightly secreted by the nephron.

Chapter Review

The entire volume of the blood is filtered through the kidneys about 300 times per day, and 99 percent of the water filtered is recovered. The GFR is influenced by hydrostatic pressure and colloid osmotic pressure. Under normal circumstances, hydrostatic pressure is significantly greater and filtration occurs. The hydrostatic pressure of the glomerulus depends on systemic blood pressure, autoregulatory mechanisms, sympathetic nervous activity, and paracrine hormones. The kidney can function normally under a wide range of blood pressures due to the autoregulatory nature of smooth muscle.

Review Questions

Exercise:

Problem:

_____ pressure must be greater on the capillary side of the filtration membrane to achieve filtration.

- a. Osmotic
- b. Hydrostatic

Solution:

B

Exercise:

Problem:

Production of urine to modify plasma makeup is the result of _____.

- a. filtration
 - b. absorption
 - c. secretion
 - d. filtration, absorption, and secretion
-

Solution:

D

Exercise:

Problem:

Systemic blood pressure must stay above 60 so that the proper amount of filtration occurs.

- a. true
- b. false

Solution:

B

Critical Thinking Questions

Exercise:

Problem: Give the formula for net filtration pressure.

Solution:

Net filtration pressure (NFP) = glomerular blood hydrostatic pressure (GBHP) – [capsular hydrostatic pressure (CHP) + blood colloid osmotic pressure (BCOP)]

Exercise:

Problem: Name at least five symptoms of kidney failure.

Solution:

Symptoms of kidney failure are weakness, lethargy, shortness of breath, widespread edema, anemia, metabolic acidosis or alkalosis, heart arrhythmias, uremia, loss of appetite, fatigue, excessive urination, and oliguria.

Glossary

glomerular filtration rate (GFR)
rate of renal filtration

inulin
plant polysaccharide injected to determine GFR; is neither secreted nor absorbed by the kidney, so its appearance in the urine is directly proportional to its filtration rate

net filtration pressure (NFP)
pressure of fluid across the glomerulus; calculated by taking the hydrostatic pressure of the capillary and subtracting the colloid osmotic pressure of the blood and the hydrostatic pressure of Bowman's capsule

systemic edema
increased fluid retention in the interstitial spaces and cells of the body; can be seen as swelling over large areas of the body, particularly the lower extremities

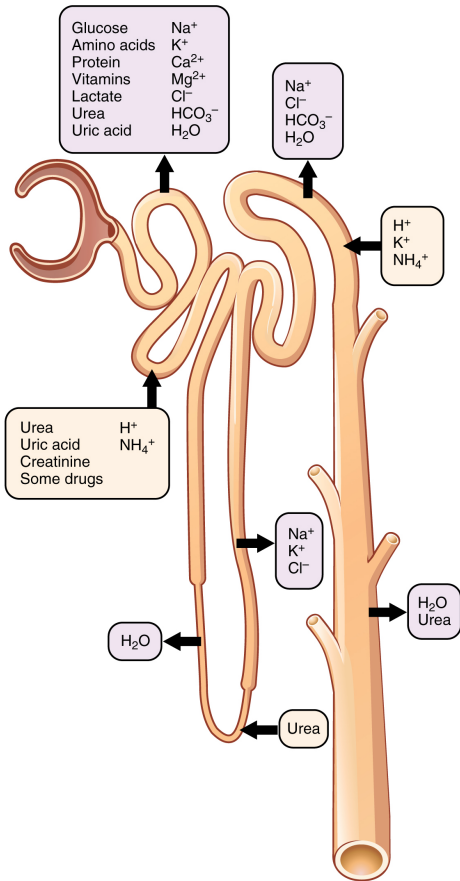
Tubular Reabsorption

By the end of this section, you will be able to:

- List specific transport mechanisms occurring in different parts of the nephron, including active transport, osmosis, facilitated diffusion, and passive electrochemical gradients
- List the different membrane proteins of the nephron, including channels, transporters, and ATPase pumps
- Compare and contrast passive and active tubular reabsorption
- Explain why the differential permeability or impermeability of specific sections of the nephron tubules is necessary for urine formation
- Describe how and where water, organic compounds, and ions are reabsorbed in the nephron
- Explain the role of the loop of Henle, the vasa recta, and the countercurrent multiplication mechanisms in the concentration of urine
- List the locations in the nephron where tubular secretion occurs

With up to 180 liters per day passing through the nephrons of the kidney, it is quite obvious that most of that fluid and its contents must be reabsorbed. That recovery occurs in the PCT, loop of Henle, DCT, and the collecting ducts ([link](#) and [link](#)). Various portions of the nephron differ in their capacity to reabsorb water and specific solutes. While much of the reabsorption and secretion occur passively based on concentration gradients, the amount of water that is reabsorbed or lost is tightly regulated. This control is exerted directly by ADH and aldosterone, and indirectly by renin. Most water is recovered in the PCT, loop of Henle, and DCT. About 10 percent (about 18 L) reaches the collecting ducts. The collecting ducts, under the influence of ADH, can recover almost all of the water passing through them, in cases of dehydration, or almost none of the water, in cases of over-hydration.

Locations of Secretion and Reabsorption in the Nephron



| Substances Secreted or Reabsorbed in the Nephron and Their Locations | | | | |
|--|--|---------------|-----|------------------|
| Substance | PCT | Loop of Henle | DCT | Collecting ducts |
| Glucose | Almost 100 percent reabsorbed; secondary active transport with Na^+ | | | |

| Substances Secreted or Reabsorbed in the Nephron and Their Locations | | | | |
|--|---|--|------------------------------|---|
| Substance | PCT | Loop of Henle | DCT | Collecting ducts |
| Oligopeptides, proteins, amino acids | Almost 100 percent reabsorbed; symport with Na ⁺ | | | |
| Vitamins | Reabsorbed | | | |
| Lactate | Reabsorbed | | | |
| Creatinine | Secreted | | | |
| Urea | 50 percent reabsorbed by diffusion; also secreted | Secretion, diffusion in descending limb | | Reabsorption in medullary collecting ducts; diffusion |
| Sodium | 65 percent actively reabsorbed | 25 percent reabsorbed in thick ascending limb; active transport | 5 percent reabsorbed; active | 5 percent reabsorbed, stimulated by aldosterone; active |
| Chloride | Reabsorbed, symport with Na ⁺ , diffusion | Reabsorbed in thin and thick ascending limb; diffusion in ascending limb | Reabsorbed; diffusion | Reabsorbed; symport |

| Substances Secreted or Reabsorbed in the Nephron and Their Locations | | | | |
|--|---|--|--------------------------------------|---|
| Substance | PCT | Loop of Henle | DCT | Collecting ducts |
| Water | 67 percent reabsorbed osmotically with solutes | 15 percent reabsorbed in descending limb; osmosis | 8 percent reabsorbed if ADH; osmosis | Variable amounts reabsorbed, controlled by ADH, osmosis |
| Bicarbonate | 80–90 percent symport reabsorption with Na^+ | Reabsorbed, symport with Na^+ and antiport with Cl^- ; in ascending limb | | Reabsorbed antiport with Cl^- |
| H^+ | Secreted; diffusion | | Secreted; active | Secreted; active |
| NH_4^+ | Secreted; diffusion | | Secreted; diffusion | Secreted; diffusion |
| HCO_3^- | Reabsorbed; diffusion | Reabsorbed; diffusion in ascending limb | Reabsorbed; diffusion | Reabsorbed; antiport with Na^+ |
| Some drugs | Secreted | | Secreted; active | Secreted; active |
| Potassium | 65 percent reabsorbed; diffusion | 20 percent reabsorbed in thick ascending limb; symport | Secreted; active | Secretion controlled by aldosterone; active |

| Substances Secreted or Reabsorbed in the Nephron and Their Locations | | | | |
|--|--|---|-----------------------|---|
| Substance | PCT | Loop of Henle | DCT | Collecting ducts |
| Calcium | Reabsorbed; diffusion | Reabsorbed in thick ascending limb; diffusion | | Reabsorbed if parathyroid hormone present; active |
| Magnesium | Reabsorbed; diffusion | Reabsorbed in thick ascending limb; diffusion | Reabsorbed | |
| Phosphate | 85 percent reabsorbed, inhibited by parathyroid hormone, diffusion | | Reabsorbed; diffusion | |

Mechanisms of Recovery

Mechanisms by which substances move across membranes for reabsorption or secretion include active transport, diffusion, facilitated diffusion, secondary active transport, and osmosis. These were discussed in an earlier chapter, and you may wish to review them.

Active transport utilizes energy, usually the energy found in a phosphate bond of ATP, to move a substance across a membrane from a low to a high concentration. It is very specific and must have an appropriately shaped receptor for the substance to be transported. An example would be the active transport of Na^+ out of a cell and K^+ into a cell by the Na^+/K^+ pump. Both ions are moved in opposite directions from a lower to a higher concentration.

Simple diffusion moves a substance from a higher to a lower concentration down its concentration gradient. It requires no energy and only needs to be soluble.

Facilitated diffusion is similar to diffusion in that it moves a substance down its concentration gradient. The difference is that it requires specific membrane receptors or channel proteins for movement. The movement of glucose and, in certain situations, Na^+ ions, is an example of facilitated diffusion. In some cases of mediated transport, two

different substances share the same channel protein port; these mechanisms are described by the terms symport and antiport.

Symport mechanisms move two or more substances in the same direction at the same time, whereas antiport mechanisms move two or more substances in opposite directions across the cell membrane. Both mechanisms may utilize concentration gradients maintained by ATP pumps. As described previously, when active transport powers the transport of another substance in this way, it is called “secondary active transport.” Glucose reabsorption in the kidneys is by secondary active transport. Na^+/K^+ ATPases on the basal membrane of a tubular cell constantly pump Na^+ out of the cell, maintaining a strong electrochemical gradient for Na^+ to move into the cell from the tubular lumen. On the luminal (apical) surface, a Na^+ /glucose symport protein assists both Na^+ and glucose movement into the cell. The cotransporter moves glucose into the cell against its concentration gradient as Na^+ moves down the electrochemical gradient created by the basal membranes Na^+/K^+ ATPases. The glucose molecule then diffuses across the basal membrane by facilitated diffusion into the interstitial space and from there into peritubular capillaries.

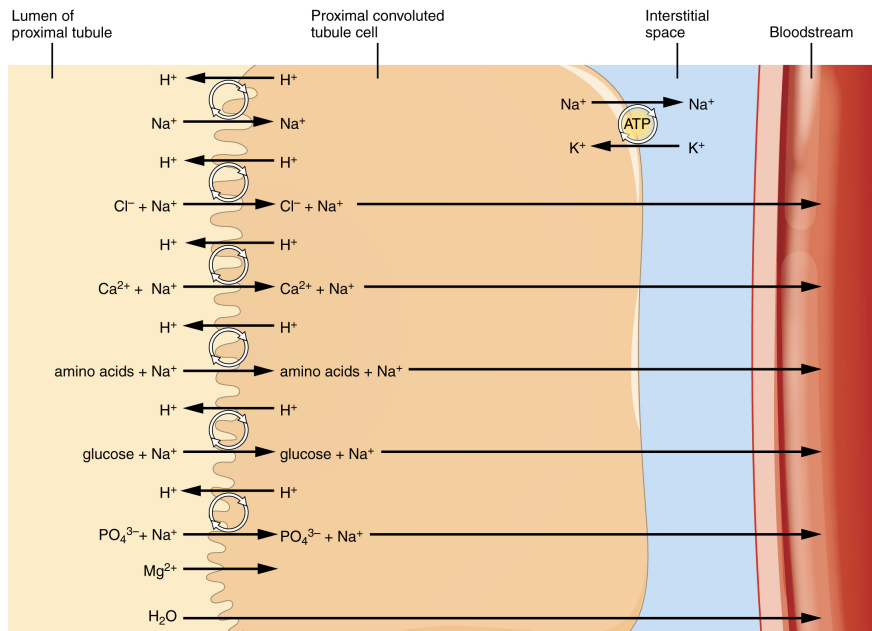
Most of the Ca^{++} , Na^+ , glucose, and amino acids must be reabsorbed by the nephron to maintain homeostatic plasma concentrations. Other substances, such as urea, K^+ , ammonia (NH_3), creatinine, and some drugs are secreted into the filtrate as waste products. Acid–base balance is maintained through actions of the lungs and kidneys: The lungs rid the body of H^+ , whereas the kidneys secrete or reabsorb H^+ and HCO_3^- ([link](#)). In the case of urea, about 50 percent is passively reabsorbed by the PCT. More is recovered by in the collecting ducts as needed. ADH induces the insertion of urea transporters and aquaporin channel proteins.

| Substances Filtered and Reabsorbed by the Kidney per 24 Hours | | | |
|---|-------------------------|---------------------------|-------------------------|
| Substance | Amount filtered (grams) | Amount reabsorbed (grams) | Amount in urine (grams) |
| Water | 180 L | 179 L | 1 L |
| Proteins | 10–20 | 10–20 | 0 |
| Chlorine | 630 | 625 | 5 |
| Sodium | 540 | 537 | 3 |
| Bicarbonate | 300 | 299.7 | 0.3 |

| Substances Filtered and Reabsorbed by the Kidney per 24 Hours | | | |
|---|-------------------------|---------------------------|-------------------------|
| Substance | Amount filtered (grams) | Amount reabsorbed (grams) | Amount in urine (grams) |
| Glucose | 180 | 180 | 0 |
| Urea | 53 | 28 | 25 |
| Potassium | 28 | 24 | 4 |
| Uric acid | 8.5 | 7.7 | 0.8 |
| Creatinine | 1.4 | 0 | 1.4 |

Reabsorption and Secretion in the PCT

The renal corpuscle filters the blood to create a filtrate that differs from blood mainly in the absence of cells and large proteins. From this point to the ends of the collecting ducts, the filtrate or forming urine is undergoing modification through secretion and reabsorption before true urine is produced. The first point at which the forming urine is modified is in the PCT. Here, some substances are reabsorbed, whereas others are secreted. Note the use of the term “reabsorbed.” All of these substances were “absorbed” in the digestive tract—99 percent of the water and most of the solutes filtered by the nephron must be reabsorbed. Water and substances that are reabsorbed are returned to the circulation by the peritubular and vasa recta capillaries. It is important to understand the difference between the glomerulus and the peritubular and vasa recta capillaries. The glomerulus has a relatively high pressure inside its capillaries and can sustain this by dilating the afferent arteriole while constricting the efferent arteriole. This assures adequate filtration pressure even as the systemic blood pressure varies. Movement of water into the peritubular capillaries and vasa recta will be influenced primarily by osmolarity and concentration gradients. Sodium is actively pumped out of the PCT into the interstitial spaces between cells and diffuses down its concentration gradient into the peritubular capillary. As it does so, water will follow passively to maintain an isotonic fluid environment inside the capillary. This is called obligatory water reabsorption, because water is “obliged” to follow the Na^+ ([link](#)).
Substances Reabsorbed and Secreted by the PCT



More substances move across the membranes of the PCT than any other portion of the nephron. Many of these substances (amino acids and glucose) use symport mechanisms for transport along with Na^+ . Antiport, active transport, diffusion, and facilitated diffusion are additional mechanisms by which substances are moved from one side of a membrane to the other. Recall that cells have two surfaces: apical and basal. The apical surface is the one facing the lumen or open space of a cavity or tube, in this case, the inside of the PCT. The basal surface of the cell faces the connective tissue base to which the cell attaches (basement membrane) or the cell membrane closer to the basement membrane if there is a stratified layer of cells. In the PCT, there is a single layer of simple cuboidal endothelial cells against the basement membrane. The numbers and particular types of pumps and channels vary between the apical and basilar surfaces. A few of the substances that are transported with Na^+ (symport mechanism) on the apical membrane include Cl^- , Ca^{++} , amino acids, glucose, and PO_4^{3-} . Sodium is actively exchanged for K^+ using ATP on the basal membrane. Most of the substances transported by a symport mechanism on the apical membrane are transported by facilitated diffusion on the basal membrane. At least three ions, K^+ , Ca^{++} , and Mg^{++} , diffuse laterally between adjacent cell membranes (transcellular).

About 67 percent of the water, Na^+ , and K^+ entering the nephron is reabsorbed in the PCT and returned to the circulation. Almost 100 percent of glucose, amino acids, and other organic substances such as vitamins are normally recovered here. Some glucose may appear in the urine if circulating glucose levels are high enough that all the glucose transporters in the PCT are saturated, so that their capacity to move glucose is exceeded (transport maximum, or T_m). In men, the maximum amount of glucose that can be recovered is about 375 mg/min, whereas in women, it is about 300 mg/min. This recovery rate translates to an arterial concentration of about 200 mg/dL. Though an exceptionally high sugar intake might cause sugar to appear briefly in the urine, the appearance of **glycosuria** usually points to type I or II diabetes mellitus. The transport of glucose from the lumen of the PCT

to the interstitial space is similar to the way it is absorbed by the small intestine. Both glucose and Na^+ bind simultaneously to the same symport proteins on the apical surface of the cell to be transported in the same direction, toward the interstitial space. Sodium moves down its electrochemical and concentration gradient into the cell and takes glucose with it. Na^+ is then actively pumped out of the cell at the basal surface of the cell into the interstitial space. Glucose leaves the cell to enter the interstitial space by facilitated diffusion. The energy to move glucose comes from the Na^+/K^+ ATPase that pumps Na^+ out of the cell on the basal surface. Fifty percent of Cl^- and variable quantities of Ca^{++} , Mg^{++} , and HPO_4^{2-} are also recovered in the PCT.

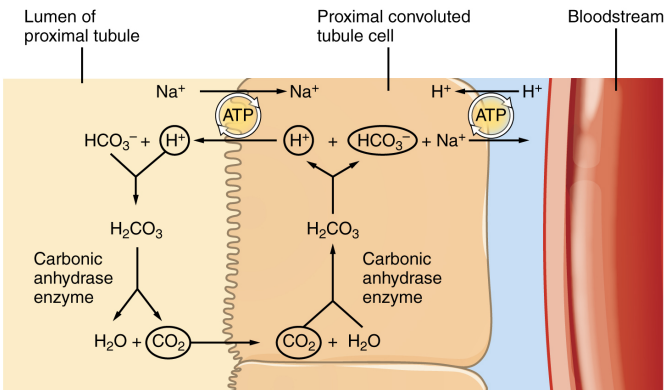
Recovery of bicarbonate (HCO_3^-) is vital to the maintenance of acid–base balance, since it is a very powerful and fast-acting buffer. An important enzyme is used to catalyze this mechanism: carbonic anhydrase (CA). This same enzyme and reaction is used in red blood cells in the transportation of CO_2 , in the stomach to produce hydrochloric acid, and in the pancreas to produce HCO_3^- to buffer acidic chyme from the stomach. In the kidney, most of the CA is located within the cell, but a small amount is bound to the brush border of the membrane on the apical surface of the cell. In the lumen of the PCT, HCO_3^- combines with hydrogen ions to form carbonic acid (H_2CO_3). This is enzymatically catalyzed into CO_2 and water, which diffuse across the apical membrane into the cell. Water can move osmotically across the lipid bilayer membrane due to the presence of aquaporin water channels. Inside the cell, the reverse reaction occurs to produce bicarbonate ions (HCO_3^-). These bicarbonate ions are cotransported with Na^+ across the basal membrane to the interstitial space around the PCT ([link](#)). At the same time this is occurring, a Na^+/H^+ antiporter excretes H^+ into the lumen, while it recovers Na^+ . Note how the hydrogen ion is recycled so that bicarbonate can be recovered. Also, note that a Na^+ gradient is created by the Na^+/K^+ pump.

Equation:



The significant recovery of solutes from the PCT lumen to the interstitial space creates an osmotic gradient that promotes water recovery. As noted before, water moves through channels created by the aquaporin proteins. These proteins are found in all cells in varying amounts and help regulate water movement across membranes and through cells by creating a passageway across the hydrophobic lipid bilayer membrane. Changing the number of aquaporin proteins in membranes of the collecting ducts also helps to regulate the osmolarity of the blood. The movement of many positively charged ions also creates an electrochemical gradient. This charge promotes the movement of negative ions toward the interstitial spaces and the movement of positive ions toward the lumen.

Reabsorption of Bicarbonate from the PCT



Reabsorption and Secretion in the Loop of Henle

The loop of Henle consists of two sections: thick and thin descending and thin and thick ascending sections. The loops of cortical nephrons do not extend into the renal medulla very far, if at all. Juxtamedullary nephrons have loops that extend variable distances, some very deep into the medulla. The descending and ascending portions of the loop are highly specialized to enable recovery of much of the Na^+ and water that were filtered by the glomerulus. As the forming urine moves through the loop, the osmolarity will change from isosmotic with blood (about 278–300 mOsmol/kg) to both a very hypertonic solution of about 1200 mOsmol/kg and a very hypotonic solution of about 100 mOsmol/kg. These changes are accomplished by osmosis in the descending limb and active transport in the ascending limb. Solutes and water recovered from these loops are returned to the circulation by way of the vasa recta.

Descending Loop

The majority of the descending loop is comprised of simple squamous epithelial cells; to simplify the function of the loop, this discussion focuses on these cells. These membranes have permanent aquaporin channel proteins that allow unrestricted movement of water from the descending loop into the surrounding interstitium as osmolarity increases from about 300 mOsmol/kg to about 1200 mOsmol/kg. This increase results in reabsorption of up to 15 percent of the water entering the nephron. Modest amounts of urea, Na^+ , and other ions are also recovered here.

Most of the solutes that were filtered in the glomerulus have now been recovered along with a majority of water, about 82 percent. As the forming urine enters the ascending loop, major adjustments will be made to the concentration of solutes to create what you perceive as urine.

Ascending Loop

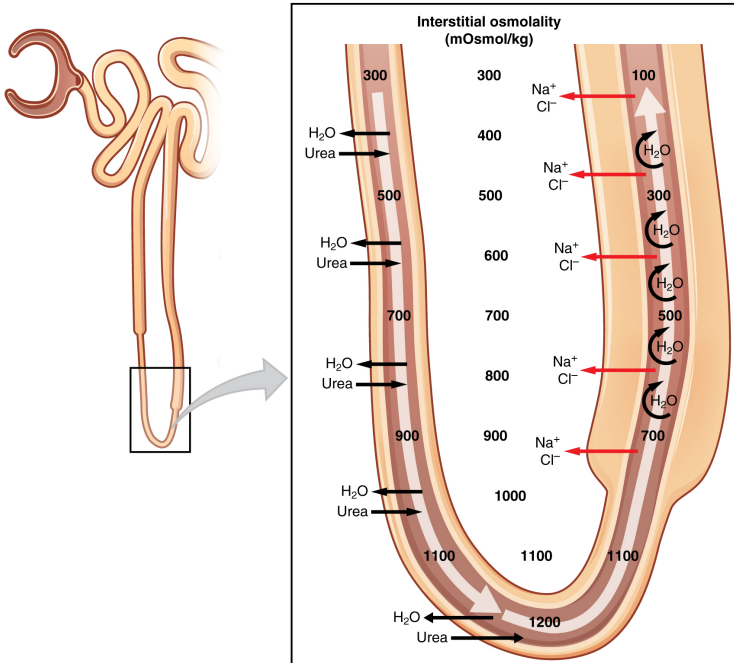
The ascending loop is made of very short thin and longer thick portions. Once again, to simplify the function, this section only considers the thick portion. The thick portion is lined with simple cuboidal epithelium without a brush border. It is completely impermeable to water due to the absence of aquaporin proteins, but ions, mainly Na^+ and Cl^- , are actively reabsorbed by a cotransport system. This has two significant effects: Removal of NaCl while retaining water leads to a hypoosmotic filtrate by the time it reaches the DCT; pumping NaCl into the interstitial space contributes to the hyperosmotic environment in the kidney medulla.

The Na^+/K^+ ATPase pumps in the basal membrane create an electrochemical gradient, allowing reabsorption of Cl^- by Na^+/Cl^- symporters in the apical membrane. At the same time that Na^+ is actively pumped from the basal side of the cell into the interstitial fluid, Cl^- follows the Na^+ from the lumen into the interstitial fluid by a paracellular route between cells through **leaky tight junctions**. These are found between cells of the ascending loop, where they allow certain solutes to move according to their concentration gradient. Most of the K^+ that enters the cell via symporters returns to the lumen (down its concentration gradient) through leaky channels in the apical membrane. Note the environment now created in the interstitial space: With the “back door exiting” K^+ , there is one Na^+ and two Cl^- ions left in the interstitium surrounding the ascending loop. Therefore, in comparison to the lumen of the loop, the interstitial space is now a negatively charged environment. This negative charge attracts cations (Na^+ , K^+ , Ca^{++} , and Mg^{++}) from the lumen via a paracellular route to the interstitial space and vasa recta.

Countercurrent Multiplier System

The structure of the loop of Henle and associated vasa recta create a **countercurrent multiplier system** ([\[link\]](#)). The countercurrent term comes from the fact that the descending and ascending loops are next to each other and their fluid flows in opposite directions (countercurrent). The multiplier term is due to the action of solute pumps that increase (multiply) the concentrations of urea and Na^+ deep in the medulla.

Countercurrent Multiplier System



As discussed above, the ascending loop actively reabsorbs NaCl out of the forming urine into the interstitial spaces. In addition, collecting ducts have urea pumps that actively pump urea into the interstitial spaces. This results in the recovery of NaCl to the circulation via the vasa recta and creates a high osmolar environment in the depths of the medulla.

Ammonia (NH_3) is a toxic byproduct of protein metabolism. It is formed as amino acids are deaminated by liver hepatocytes. That means that the amine group, NH_2 , is removed from amino acids as they are broken down. Most of the resulting ammonia is converted into urea by liver hepatocytes. Urea is not only less toxic but is utilized to aid in the recovery of water by the loop of Henle and collecting ducts. At the same time that water is freely diffusing out of the descending loop through aquaporin channels into the interstitial spaces of the medulla, urea freely diffuses into the lumen of the descending loop as it descends deeper into the medulla, much of it to be reabsorbed from the forming urine when it reaches the collecting duct. Thus, the movement of Na^+ and urea into the interstitial spaces by these mechanisms creates the hyperosmotic environment of the medulla. The net result of this countercurrent multiplier system is to recover both water and Na^+ in the circulation.

The amino acid glutamine can be deaminated by the kidney. As NH_2 from the amino acid is converted into NH_3 and pumped into the lumen of the PCT, Na^+ and HCO_3^- are excreted into the interstitial fluid of the renal pyramid via a symport mechanism. When this process occurs in the cells of the PCT, the added benefit is a net loss of a hydrogen ion (complexed to ammonia to form the weak acid NH_4^+) in the urine and a gain of a bicarbonate ion (HCO_3^-) in the blood. Ammonia and bicarbonate are exchanged in a one-to-one ratio. This exchange is yet another means by which the body can buffer and excrete acid. The presence of aquaporin channels in the descending loop allows prodigious quantities of water to leave the loop and enter the hyperosmolar interstitium of the pyramid, where it is returned to the

circulation by the vasa recta. As the loop turns to become the ascending loop, there is an absence of aquaporin channels, so water cannot leave the loop. However, in the basal membrane of cells of the thick ascending loop, ATPase pumps actively remove Na^+ from the cell. A $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ symporter in the apical membrane passively allows these ions to enter the cell cytoplasm from the lumen of the loop down a concentration gradient created by the pump. This mechanism works to dilute the fluid of the ascending loop ultimately to approximately 50–100 mOsmol/L.

At the transition from the DCT to the collecting duct, about 20 percent of the original water is still present and about 10 percent of the sodium. If no other mechanism for water reabsorption existed, about 20–25 liters of urine would be produced. Now consider what is happening in the adjacent capillaries, the vasa recta. They are recovering both solutes and water at a rate that preserves the countercurrent multiplier system. In general, blood flows slowly in capillaries to allow time for exchange of nutrients and wastes. In the vasa recta particularly, this rate of flow is important for two additional reasons. The flow must be slow to allow blood cells to lose and regain water without either crenating or bursting. Second, a rapid flow would remove too much Na^+ and urea, destroying the osmolar gradient that is necessary for the recovery of solutes and water. Thus, by flowing slowly to preserve the countercurrent mechanism, as the vasa recta descend, Na^+ and urea are freely able to enter the capillary, while water freely leaves; as they ascend, Na^+ and urea are secreted into the surrounding medulla, while water reenters and is removed.

Note:



Watch this [video](#) to learn about the countercurrent multiplier system.

Reabsorption and Secretion in the Distal Convoluted Tubule

Approximately 80 percent of filtered water has been recovered by the time the dilute forming urine enters the DCT. The DCT will recover another 10–15 percent before the forming urine enters the collecting ducts. Aldosterone increases the amount of Na^+/K^+ ATPase in the basal membrane of the DCT and collecting duct. The movement of Na^+ out of the lumen of the collecting duct creates a negative charge that promotes the movement of Cl^- out of the lumen into the interstitial space by a paracellular route across tight junctions. Peritubular capillaries receive the solutes and water, returning them to the circulation.

Cells of the DCT also recover Ca^{++} from the filtrate. Receptors for parathyroid hormone (PTH) are found in DCT cells and when bound to PTH, induce the insertion of calcium channels on their luminal surface. The channels enhance Ca^{++} recovery from the forming urine. In addition, as Na^+ is pumped out of the cell, the resulting electrochemical gradient attracts Ca^{++} into the cell. Finally, calcitriol (1,25 dihydroxyvitamin D, the active form of vitamin D) is very important for calcium recovery. It induces the production of calcium-binding proteins that transport Ca^{++} into the cell. These binding proteins are also important for the movement of calcium inside the cell and aid in exocytosis of calcium across the basolateral membrane. Any Ca^{++} not reabsorbed at this point is lost in the urine.

Collecting Ducts and Recovery of Water

Solutes move across the membranes of the collecting ducts, which contain two distinct cell types, principal cells and intercalated cells. A **principal cell** possesses channels for the recovery or loss of sodium and potassium. An **intercalated cell** secretes or absorbs acid or bicarbonate. As in other portions of the nephron, there is an array of micromachines (pumps and channels) on display in the membranes of these cells.

Regulation of urine volume and osmolarity are major functions of the collecting ducts. By varying the amount of water that is recovered, the collecting ducts play a major role in maintaining the body's normal osmolarity. If the blood becomes hyperosmotic, the collecting ducts recover more water to dilute the blood; if the blood becomes hyposmotic, the collecting ducts recover less of the water, leading to concentration of the blood. Another way of saying this is: If plasma osmolarity rises, more water is recovered and urine volume decreases; if plasma osmolarity decreases, less water is recovered and urine volume increases. This function is regulated by the posterior pituitary hormone ADH (vasopressin). With mild dehydration, plasma osmolarity rises slightly. This increase is detected by osmoreceptors in the hypothalamus, which stimulates the release of ADH from the posterior pituitary. If plasma osmolarity decreases slightly, the opposite occurs.

When stimulated by ADH, aquaporin channels are inserted into the apical membrane of principal cells, which line the collecting ducts. As the ducts descend through the medulla, the osmolarity surrounding them increases (due to the countercurrent mechanisms described above). If aquaporin water channels are present, water will be osmotically pulled from the collecting duct into the surrounding interstitial space and into the peritubular capillaries. Therefore, the final urine will be more concentrated. If less ADH is secreted, fewer aquaporin channels are inserted and less water is recovered, resulting in dilute urine. By altering the number of aquaporin channels, the volume of water recovered or lost is altered. This, in turn, regulates the blood osmolarity, blood pressure, and osmolarity of the urine.

As Na^+ is pumped from the forming urine, water is passively recaptured for the circulation; this preservation of vascular volume is critically important for the maintenance of a normal blood pressure. Aldosterone is secreted by the adrenal cortex in response to angiotensin II stimulation. As an extremely potent vasoconstrictor, angiotensin II functions immediately

to increase blood pressure. By also stimulating aldosterone production, it provides a longer-lasting mechanism to support blood pressure by maintaining vascular volume (water recovery).

In addition to receptors for ADH, principal cells have receptors for the steroid hormone aldosterone. While ADH is primarily involved in the regulation of water recovery, aldosterone regulates Na^+ recovery. Aldosterone stimulates principal cells to manufacture luminal Na^+ and K^+ channels as well as Na^+/K^+ ATPase pumps on the basal membrane of the cells. When aldosterone output increases, more Na^+ is recovered from the forming urine and water follows the Na^+ passively. As the pump recovers Na^+ for the body, it is also pumping K^+ into the forming urine, since the pump moves K^+ in the opposite direction. When aldosterone decreases, more Na^+ remains in the forming urine and more K^+ is recovered in the circulation. Symport channels move Na^+ and Cl^- together. Still other channels in the principal cells secrete K^+ into the collecting duct in direct proportion to the recovery of Na^+ .

Intercalated cells play significant roles in regulating blood pH. Intercalated cells reabsorb K^+ and HCO_3^- while secreting H^+ . This function lowers the acidity of the plasma while increasing the acidity of the urine.

Chapter Review

The kidney regulates water recovery and blood pressure by producing the enzyme renin. It is renin that starts a series of reactions, leading to the production of the vasoconstrictor angiotensin II and the salt-retaining steroid aldosterone. Water recovery is also powerfully and directly influenced by the hormone ADH. Even so, it only influences the last 10 percent of water available for recovery after filtration at the glomerulus, because 90 percent of water is recovered before reaching the collecting ducts. Depending on the body's fluid status at any given time, the collecting ducts can recover none or almost all of the water reaching them.

Mechanisms of solute recovery include active transport, simple diffusion, and facilitated diffusion. Most filtered substances are reabsorbed. Urea, NH_3 , creatinine, and some drugs are filtered or secreted as wastes. H^+ and HCO_3^- are secreted or reabsorbed as needed to maintain acid–base balance. Movement of water from the glomerulus is primarily due to pressure, whereas that of peritubular capillaries and vasa recta is due to osmolarity and concentration gradients. The PCT is the most metabolically active part of the nephron and uses a wide array of protein micromachines to maintain homeostasis—symporters, antiporters, and ATPase active transporters—in conjunction with diffusion, both simple and facilitated. Almost 100 percent of glucose, amino acids, and vitamins are recovered in the PCT. Bicarbonate (HCO_3^-) is recovered using the same enzyme, carbonic anhydrase (CA), found in erythrocytes. The recovery of solutes creates an osmotic gradient to promote the recovery of water. The descending loop of the juxtaglomerular nephrons reaches an osmolarity of up to 1200 mOsmol/kg, promoting the recovery of water. The ascending loop is impervious to water but actively recovers Na^+ , reducing filtrate osmolarity to 50–100

mOsmol/kg. The descending and ascending loop and vasa recta form a countercurrent multiplier system to increase Na^+ concentration in the kidney medulla. The collecting ducts actively pump urea into the medulla, further contributing to the high osmotic environment. The vasa recta recover the solute and water in the medulla, returning them to the circulation. Nearly 90 percent of water is recovered before the forming urine reaches the DCT, which will recover another 10 percent. Calcium recovery in the DCT is influenced by PTH and active vitamin D. In the collecting ducts, ADH stimulates aquaporin channel insertion to increase water recovery and thereby regulate osmolarity of the blood. Aldosterone stimulates Na^+ recovery by the collecting duct.

Review Questions

Exercise:

Problem: Aquaporin channels are only found in the collecting duct.

- a. true
- b. false

Solution:

B

Exercise:

Problem: Most absorption and secretion occurs in this part of the nephron.

- a. proximal convoluted tubule
- b. descending loop of Henle
- c. ascending loop of Henle
- d. distal convoluted tubule
- e. collecting ducts

Solution:

A

Exercise:

Problem: The fine tuning of water recovery or disposal occurs in _____.

- a. the proximal convoluted tubule
- b. the collecting ducts

- c. the ascending loop of Henle
- d. the distal convoluted tubule

Solution:

B

Critical Thinking Questions

Exercise:

Problem:

Which vessels and what part of the nephron are involved in countercurrent multiplication?

Solution:

The vasa recta and loop of Henle are involved in countercurrent multiplication.

Exercise:

Problem:

Give the approximate osmolarity of fluid in the proximal convoluted tubule, deepest part of the loop of Henle, distal convoluted tubule, and the collecting ducts.

Solution:

The approximate osmolarities are: CT = 300; deepest loop = 1200; DCT = 100; and collecting ducts = 100–1200.

Glossary

countercurrent multiplier system

involves the descending and ascending loops of Henle directing forming urine in opposing directions to create a concentration gradient when combined with variable permeability and sodium pumping

glycosuria

presence of glucose in the urine; caused by high blood glucose levels that exceed the ability of the kidneys to reabsorb the glucose; usually the result of untreated or poorly controlled diabetes mellitus

intercalated cell

specialized cell of the collecting ducts that secrete or absorb acid or bicarbonate;
important in acid–base balance

leaky tight junctions

tight junctions in which the sealing strands of proteins between the membranes of adjacent cells are fewer in number and incomplete; allows limited intercellular movement of solvent and solutes

principal cell

found in collecting ducts and possess channels for the recovery or loss of sodium and potassium; under the control of aldosterone; also have aquaporin channels under ADH control to regulate recovery of water

Regulation of Renal Blood Flow

By the end of this section, you will be able to:

- Describe the myogenic and tubuloglomerular feedback mechanisms and explain how they affect urine volume and composition
- Describe the function of the juxtaglomerular apparatus

It is vital that the flow of blood through the kidney be at a suitable rate to allow for filtration. This rate determines how much solute is retained or discarded, how much water is retained or discarded, and ultimately, the osmolarity of blood and the blood pressure of the body.

Sympathetic Nerves

The kidneys are innervated by the sympathetic neurons of the autonomic nervous system via the celiac plexus and splanchnic nerves. Reduction of sympathetic stimulation results in vasodilation and increased blood flow through the kidneys during resting conditions. When the frequency of action potentials increases, the arteriolar smooth muscle constricts (vasoconstriction), resulting in diminished glomerular flow, so less filtration occurs. Under conditions of stress, sympathetic nervous activity increases, resulting in the direct vasoconstriction of afferent arterioles (norepinephrine effect) as well as stimulation of the adrenal medulla. The adrenal medulla, in turn, produces a generalized vasoconstriction through the release of epinephrine. This includes vasoconstriction of the afferent arterioles, further reducing the volume of blood flowing through the kidneys. This process redirects blood to other organs with more immediate needs. If blood pressure falls, the sympathetic nerves will also stimulate the release of renin. Additional renin increases production of the powerful vasoconstrictor angiotensin II. Angiotensin II, as discussed above, will also stimulate aldosterone production to augment blood volume through retention of more Na^+ and water. Only a 10 mm Hg pressure differential across the glomerulus is required for normal GFR, so very small changes in afferent arterial pressure significantly increase or decrease GFR.

Autoregulation

The kidneys are very effective at regulating the rate of blood flow over a wide range of blood pressures. Your blood pressure will decrease when you are relaxed or sleeping. It will increase when exercising. Yet, despite these changes, the filtration rate through the kidney will change very little. This is due to two internal autoregulatory mechanisms that operate without outside influence: the myogenic mechanism and the tubuloglomerular feedback mechanism.

Arteriole Myogenic Mechanism

The **myogenic mechanism** regulating blood flow within the kidney depends upon a characteristic shared by most smooth muscle cells of the body. When you stretch a smooth muscle cell, it contracts; when you stop, it relaxes, restoring its resting length. This mechanism works in the afferent arteriole that supplies the glomerulus. When blood pressure increases, smooth muscle cells in the wall of the arteriole are stretched and respond by contracting to resist the pressure, resulting in little change in flow. When blood pressure drops, the same smooth muscle cells relax to lower resistance, allowing a continued even flow of blood.

Tubuloglomerular Feedback

The **tubuloglomerular feedback** mechanism involves the JGA and a paracrine signaling mechanism utilizing ATP, adenosine, and nitric oxide (NO). This mechanism stimulates either contraction or relaxation of afferent arteriolar smooth muscle cells ([\[link\]](#)). Recall that the DCT is in intimate contact with the afferent and efferent arterioles of the glomerulus. Specialized macula densa cells in this segment of the tubule respond to changes in the fluid flow rate and Na^+ concentration. As GFR increases, there is less time for NaCl to be reabsorbed in the PCT, resulting in higher osmolarity in the filtrate. The increased fluid movement more strongly deflects single nonmotile cilia on macula densa cells. This increased osmolarity of the forming urine, and the greater flow rate within the DCT, activates macula densa cells to respond by releasing ATP and adenosine (a

metabolite of ATP). ATP and adenosine act locally as paracrine factors to stimulate the myogenic juxtaglomerular cells of the afferent arteriole to constrict, slowing blood flow and reducing GFR. Conversely, when GFR decreases, less Na^+ is in the forming urine, and most will be reabsorbed before reaching the macula densa, which will result in decreased ATP and adenosine, allowing the afferent arteriole to dilate and increase GFR. NO has the opposite effect, relaxing the afferent arteriole at the same time ATP and adenosine are stimulating it to contract. Thus, NO fine-tunes the effects of adenosine and ATP on GFR.

| Paracrine Mechanisms Controlling Glomerular Filtration Rate | | | |
|--|------------------------|--|----------------------------|
| Change in GFR | NaCl Absorption | Role of ATP and adenosine/Role of NO | Effect on GFR |
| Increased GFR | Tubular NaCl increases | ATP and adenosine increase, causing vasoconstriction | Vasoconstriction slows GFR |
| Decreased GFR | Tubular NaCl decreases | ATP and adenosine decrease, causing vasodilation | Vasodilation increases GFR |
| Increased GFR | Tubular NaCl increases | NO increases, causing vasodilation | Vasodilation increases GFR |

| Paracrine Mechanisms Controlling Glomerular Filtration Rate | | | |
|---|------------------------|--|--------------------------------|
| Change in GFR | NaCl Absorption | Role of ATP and adenosine/Role of NO | Effect on GFR |
| Decreased GFR | Tubular NaCl decreases | NO decreases, causing vasoconstriction | Vasoconstriction decreases GFR |

Chapter Review

The kidneys are innervated by sympathetic nerves of the autonomic nervous system. Sympathetic nervous activity decreases blood flow to the kidney, making more blood available to other areas of the body during times of stress. The arteriolar myogenic mechanism maintains a steady blood flow by causing arteriolar smooth muscle to contract when blood pressure increases and causing it to relax when blood pressure decreases. Tubuloglomerular feedback involves paracrine signaling at the JGA to cause vasoconstriction or vasodilation to maintain a steady rate of blood flow.

Review Questions

Exercise:

Problem:

Vasodilation of blood vessels to the kidneys is due to _____.

- a. more frequent action potentials
- b. less frequent action potentials

Solution:

B

Exercise:

Problem:

When blood pressure increases, blood vessels supplying the kidney will _____ to mount a steady rate of filtration.

- a. contract
- b. relax

Solution:

A

Exercise:

Problem: Which of these three paracrine chemicals cause vasodilation?

- a. ATP
- b. adenosine
- c. nitric oxide

Solution:

C

Critical Thinking Questions

Exercise:

Problem:

Explain what happens to Na^+ concentration in the nephron when GFR increases.

Solution:

Sodium concentration in the filtrate increases when GFR increases; it will decrease when GFR decreases.

Exercise:

Problem:

If you want the kidney to excrete more Na^+ in the urine, what do you want the blood flow to do?

Solution:

To excrete more Na^+ in the urine, increase the flow rate.

Glossary

myogenic mechanism

mechanism by which smooth muscle responds to stretch by contracting; an increase in blood pressure causes vasoconstriction and a decrease in blood pressure causes vasodilation so that blood flow downstream remains steady

tubuloglomerular feedback

feedback mechanism involving the JGA; macula densa cells monitor Na^+ concentration in the terminal portion of the ascending loop of Henle and act to cause vasoconstriction or vasodilation of afferent and efferent arterioles to alter GFR

Endocrine Regulation of Kidney Function

By the end of this section, you will be able to:

- Describe how each of the following functions in the extrinsic control of GFR: renin–angiotensin mechanism, natriuretic peptides, and sympathetic adrenergic activity
- Describe how each of the following works to regulate reabsorption and secretion, so as to affect urine volume and composition: renin–angiotensin system, aldosterone, antidiuretic hormone, and natriuretic peptides
- Name and define the roles of other hormones that regulate kidney control

Several hormones have specific, important roles in regulating kidney function. They act to stimulate or inhibit blood flow. Some of these are endocrine, acting from a distance, whereas others are paracrine, acting locally.

Renin–Angiotensin–Aldosterone

Renin is an enzyme that is produced by the granular cells of the afferent arteriole at the JGA. It enzymatically converts angiotensinogen (made by the liver, freely circulating) into angiotensin I. Its release is stimulated by prostaglandins and NO from the JGA in response to decreased extracellular fluid volume.

ACE is not a hormone but it is functionally important in regulating systemic blood pressure and kidney function. It is produced in the lungs but binds to the surfaces of endothelial cells in the afferent arterioles and glomerulus. It enzymatically converts inactive angiotensin I into active angiotensin II. ACE is important in raising blood pressure. People with high blood pressure are sometimes prescribed ACE inhibitors to lower their blood pressure.

Angiotensin II is a potent vasoconstrictor that plays an immediate role in the regulation of blood pressure. It acts systemically to cause vasoconstriction as well as constriction of both the afferent and efferent

arterioles of the glomerulus. In instances of blood loss or dehydration, it reduces both GFR and renal blood flow, thereby limiting fluid loss and preserving blood volume. Its release is usually stimulated by decreases in blood pressure, and so the preservation of adequate blood pressure is its primary role.

Aldosterone, often called the “salt-retaining hormone,” is released from the adrenal cortex in response to angiotensin II or directly in response to increased plasma K^+ . It promotes Na^+ reabsorption by the nephron, promoting the retention of water. It is also important in regulating K^+ , promoting its excretion. (This dual effect on two minerals and its origin in the adrenal cortex explains its designation as a mineralocorticoid.) As a result, renin has an immediate effect on blood pressure due to angiotensin II–stimulated vasoconstriction and a prolonged effect through Na^+ recovery due to aldosterone. At the same time that aldosterone causes increased recovery of Na^+ , it also causes greater loss of K^+ . Progesterone is a steroid that is structurally similar to aldosterone. It binds to the aldosterone receptor and weakly stimulates Na^+ reabsorption and increased water recovery. This process is unimportant in men due to low levels of circulating progesterone. It may cause increased retention of water during some periods of the menstrual cycle in women when progesterone levels increase.

Antidiuretic Hormone (ADH)

Diuretics are drugs that can increase water loss by interfering with the recapture of solutes and water from the forming urine. They are often prescribed to lower blood pressure. Coffee, tea, and alcoholic beverages are familiar diuretics. ADH, a 9-amino acid peptide released by the posterior pituitary, works to do the exact opposite. It promotes the recovery of water, decreases urine volume, and maintains plasma osmolarity and blood pressure. It does so by stimulating the movement of aquaporin proteins into the apical cell membrane of principal cells of the collecting ducts to form water channels, allowing the transcellular movement of water from the lumen of the collecting duct into the interstitial space in the medulla of the kidney by osmosis. From there, it enters the vasa recta capillaries to return

to the circulation. Water is attracted by the high osmotic environment of the deep kidney medulla.

Endothelin

Endothelins, 21-amino acid peptides, are extremely powerful vasoconstrictors. They are produced by endothelial cells of the renal blood vessels, mesangial cells, and cells of the DCT. Hormones stimulating endothelin release include angiotensin II, bradykinin, and epinephrine. They do not typically influence blood pressure in healthy people. On the other hand, in people with diabetic kidney disease, endothelin is chronically elevated, resulting in sodium retention. They also diminish GFR by damaging the podocytes and by potently vasoconstricting both the afferent and efferent arterioles.

Natriuretic Hormones

Natriuretic hormones are peptides that stimulate the kidneys to excrete sodium—an effect opposite that of aldosterone. Natriuretic hormones act by inhibiting aldosterone release and therefore inhibiting Na^+ recovery in the collecting ducts. If Na^+ remains in the forming urine, its osmotic force will cause a concurrent loss of water. Natriuretic hormones also inhibit ADH release, which of course will result in less water recovery. Therefore, natriuretic peptides inhibit both Na^+ and water recovery. One example from this family of hormones is atrial natriuretic hormone (ANH), a 28-amino acid peptide produced by heart atria in response to over-stretching of the atrial wall. The over-stretching occurs in persons with elevated blood pressure or heart failure. It increases GFR through concurrent vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole. These events lead to an increased loss of water and sodium in the forming urine. It also decreases sodium reabsorption in the DCT. There is also B-type natriuretic peptide (BNP) of 32 amino acids produced in the ventricles of the heart. It has a 10-fold lower affinity for its receptor, so its effects are less than those of ANH. Its role may be to provide “fine tuning” for the regulation of blood pressure. BNP’s longer biologic half-life makes it a good diagnostic marker of congestive heart failure ([link](#)).

Parathyroid Hormone

Parathyroid hormone (PTH) is an 84-amino acid peptide produced by the parathyroid glands in response to decreased circulating Ca^{++} levels. Among its targets is the PCT, where it stimulates the hydroxylation of calcidiol to calcitriol (1,25-hydroxycholecalciferol, the active form of vitamin D). It also blocks reabsorption of phosphate (PO_3^-), causing its loss in the urine. The retention of phosphate would result in the formation of calcium phosphate in the plasma, reducing circulating Ca^{++} levels. By ridding the blood of phosphate, higher circulating Ca^{++} levels are permitted.

Major Hormones That Influence GFR and RBF

| | Stimulus | Effect on GFR | Effect on RBF |
|--|--|---------------|---------------|
| VASOCONSTRICTORS | | | |
| Sympathetic nerves (epinephrine and norepinephrine) | ↓ ECFV | ↓ | ↓ |
| Angiotensin II | ↓ ECFV | ↓ | ↓ |
| Endothelin | ↑ Stretch, bradykinin, angiotensin II, epinephrine ↓ ECFV | ↓ | ↓ |
| VASODILATORS | | | |
| Prostaglandins (PGE1, PGE2, and PGI2) | ↓ ECFV ↑ shear stress, angiotensin II | No change/↑ | ↑ |
| Nitric oxide (NO) | ↑ shear stress, acetylcholine, histamine, bradykinin, ATP, adenosine | ↑ | ↑ |
| Bradykinin | Prostaglandins, ↓ ACE | ↑ | ↑ |
| Natriuretic peptides (ANP, B-type) | ↑ ECFV | ↑ | No change |
| ACE = angiotensin-converting enzyme; ECFV = extracellular fluid volume; GFR = glomerular filtration rate; RBF = renal blood flow; ANP = atrial natriuretic peptide; B-type = ventricular natriuretic peptide | | | |

Chapter Review

Endocrine hormones act from a distance and paracrine hormones act locally. The renal enzyme renin converts angiotensinogen into angiotensin I. The lung enzyme, ACE, converts angiotensin I into active angiotensin II. Angiotensin II is an active vasoconstrictor that increases blood pressure. Angiotensin II also stimulates aldosterone release from the adrenal cortex, causing the collecting duct to retain Na^+ , which promotes water retention and a longer-term rise in blood pressure. ADH promotes water recovery by

the collecting ducts by stimulating the insertion of aquaporin water channels into cell membranes. Endothelins are elevated in cases of diabetic kidney disease, increasing Na^+ retention and decreasing GFR. Natriuretic hormones, released primarily from the atria of the heart in response to stretching of the atrial walls, stimulate Na^+ excretion and thereby decrease blood pressure. PTH stimulates the final step in the formation of active vitamin D3 and reduces phosphate reabsorption, resulting in higher circulating Ca^{++} levels.

Review Questions

Exercise:

Problem:

What hormone directly opposes the actions of natriuretic hormones?

- a. renin
- b. nitric oxide
- c. dopamine
- d. aldosterone

Solution:

D

Exercise:

Problem: Which of these is a vasoconstrictor?

- a. nitric oxide
- b. natriuretic hormone
- c. bradykinin
- d. angiotensin II

Solution:

D

Exercise:

Problem:

What signal causes the heart to secrete atrial natriuretic hormone?

- a. increased blood pressure
- b. decreased blood pressure
- c. increased Na^+ levels
- d. decreased Na^+ levels

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

What organs produce which hormones or enzymes in the renin–angiotensin system?

Solution:

The liver produces angiotensinogen, the lungs produce ACE, and the kidneys produce renin.

Exercise:

Problem: PTH affects absorption and reabsorption of what?

Solution:

PTH affects absorption and reabsorption of calcium.

Glossary

endothelins

group of vasoconstrictive, 21-amino acid peptides; produced by endothelial cells of the renal blood vessels, mesangial cells, and cells of the DCT

Regulation of Fluid Volume and Composition

By the end of this section, you will be able to:

- Explain the mechanism of action of diuretics
- Explain why the differential permeability or impermeability of specific sections of the nephron tubules is necessary for urine formation

The major hormones influencing total body water are ADH, aldosterone, and ANH. Circumstances that lead to fluid depletion in the body include blood loss and dehydration. Homeostasis requires that volume and osmolarity be preserved. Blood volume is important in maintaining sufficient blood pressure, and there are nonrenal mechanisms involved in its preservation, including vasoconstriction, which can act within seconds of a drop in pressure. Thirst mechanisms are also activated to promote the consumption of water lost through respiration, evaporation, or urination. Hormonal mechanisms are activated to recover volume while maintaining a normal osmotic environment. These mechanisms act principally on the kidney.

Volume-sensing Mechanisms

The body cannot directly measure blood volume, but blood pressure can be measured. Blood pressure often reflects blood volume and is measured by baroreceptors in the aorta and carotid sinuses. When blood pressure increases, baroreceptors send more frequent action potentials to the central nervous system, leading to widespread vasodilation. Included in this vasodilation are the afferent arterioles supplying the glomerulus, resulting in increased GFR, and water loss by the kidneys. If pressure decreases, fewer action potentials travel to the central nervous system, resulting in more sympathetic stimulation-producing vasoconstriction, which will result in decreased filtration and GFR, and water loss.

Decreased blood pressure is also sensed by the granular cells in the afferent arteriole of the JGA. In response, the enzyme renin is released. You saw earlier in the chapter that renin activity leads to an almost immediate rise in blood pressure as activated angiotensin II produces vasoconstriction. The rise in pressure is sustained by the aldosterone effects initiated by

angiotensin II; this includes an increase in Na^+ retention and water volume. As an aside, late in the menstrual cycle, progesterone has a modest influence on water retention. Due to its structural similarity to aldosterone, progesterone binds to the aldosterone receptor in the collecting duct of the kidney, causing the same, albeit weaker, effect on Na^+ and water retention.

Cardiomyocytes of the atria also respond to greater stretch (as blood pressure rises) by secreting ANH. ANH opposes the action of aldosterone by inhibiting the recovery of Na^+ by the DCT and collecting ducts. More Na^+ is lost, and as water follows, total blood volume and pressure decline. In low-pressure states, ANH does not seem to have much effect.

ADH is also called vasopressin. Early researchers found that in cases of unusually high secretion of ADH, the hormone caused vasoconstriction (vasopressor activity, hence the name). Only later were its antidiuretic properties identified. Synthetic ADH is still used occasionally to stem life-threatening esophagus bleeding in alcoholics.

When blood volume drops 5–10 percent, causing a decrease in blood pressure, there is a rapid and significant increase in ADH release from the posterior pituitary. Immediate vasoconstriction to increase blood pressure is the result. ADH also causes activation of aquaporin channels in the collecting ducts to affect the recovery of water to help restore vascular volume.

Diuretics and Fluid Volume

A **diuretic** is a compound that increases urine volume. Three familiar drinks contain diuretic compounds: coffee, tea, and alcohol. The caffeine in coffee and tea works by promoting vasodilation in the nephron, which increases GFR. Alcohol increases GFR by inhibiting ADH release from the posterior pituitary, resulting in less water recovery by the collecting duct. In cases of high blood pressure, diuretics may be prescribed to reduce blood volume and, thereby, reduce blood pressure. The most frequently prescribed anti-hypertensive diuretic is hydrochlorothiazide. It inhibits the Na^+/Cl^- symporter in the DCT and collecting duct. The result is a loss of Na^+ with water following passively by osmosis.

Osmotic diuretics promote water loss by osmosis. An example is the indigestible sugar mannitol, which is most often administered to reduce brain swelling after head injury. However, it is not the only sugar that can produce a diuretic effect. In cases of poorly controlled diabetes mellitus, glucose levels exceed the capacity of the tubular glucose symporters, resulting in glucose in the urine. The unrecovered glucose becomes a powerful osmotic diuretic. Classically, in the days before glucose could be detected in the blood and urine, clinicians identified diabetes mellitus by the three Ps: polyuria (diuresis), polydipsia (increased thirst), and polyphagia (increased hunger).

Regulation of Extracellular Na^+

Sodium has a very strong osmotic effect and attracts water. It plays a larger role in the osmolarity of the plasma than any other circulating component of the blood. If there is too much Na^+ present, either due to poor control or excess dietary consumption, a series of metabolic problems ensue. There is an increase in total volume of water, which leads to hypertension (high blood pressure). Over a long period, this increases the risk of serious complications such as heart attacks, strokes, and aneurysms. It can also contribute to system-wide edema (swelling).

Mechanisms for regulating Na^+ concentration include the renin–angiotensin–aldosterone system and ADH (see [\[link\]](#)). Aldosterone stimulates the uptake of Na^+ on the apical cell membrane of cells in the DCT and collecting ducts, whereas ADH helps to regulate Na^+ concentration indirectly by regulating the reabsorption of water.

Regulation of Extracellular K^+

Potassium is present in a 30-fold greater concentration inside the cell than outside the cell. A generalization can be made that K^+ and Na^+ concentrations will move in opposite directions. When more Na^+ is reabsorbed, more K^+ is secreted; when less Na^+ is reabsorbed (leading to excretion by the kidney), more K^+ is retained. When aldosterone causes a recovery of Na^+ in the nephron, a negative electrical gradient is created that promotes the secretion of K^+ and Cl^- into the lumen.

Regulation of Cl^-

Chloride is important in acid–base balance in the extracellular space and has other functions, such as in the stomach, where it combines with hydrogen ions in the stomach lumen to form hydrochloric acid, aiding digestion. Its close association with Na^+ in the extracellular environment makes it the dominant anion of this compartment, and its regulation closely mirrors that of Na^+ .

Regulation of Ca^{++} and Phosphate

The parathyroid glands monitor and respond to circulating levels of Ca^{++} in the blood. When levels drop too low, PTH is released to stimulate the DCT to reabsorb Ca^{++} from the forming urine. When levels are adequate or high, less PTH is released and more Ca^{++} remains in the forming urine to be lost. Phosphate levels move in the opposite direction. When Ca^{++} levels are low, PTH inhibits reabsorption of HPO_4^{2-} so that its blood level drops, allowing Ca^{++} levels to rise. PTH also stimulates the renal conversion of calcidiol into calcitriol, the active form of vitamin D. Calcitriol then stimulates the intestines to absorb more Ca^{++} from the diet.

Regulation of H^+ , Bicarbonate, and pH

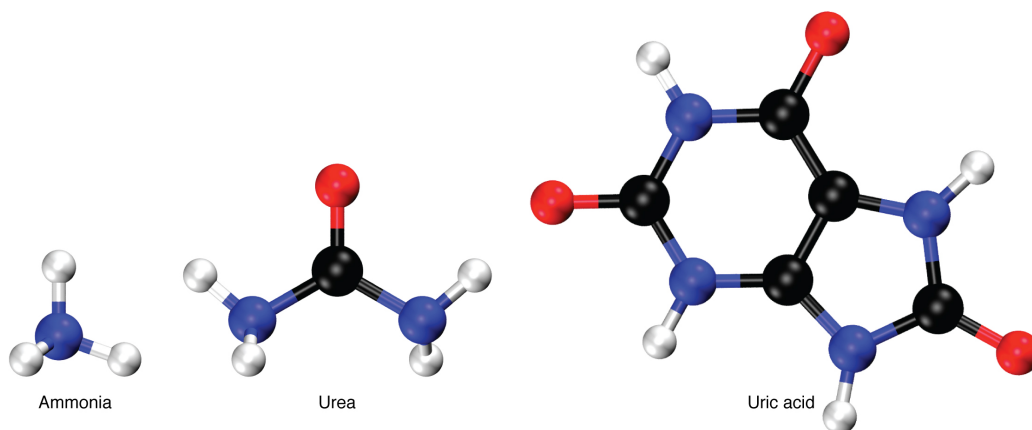
The acid–base homeostasis of the body is a function of chemical buffers and physiologic buffering provided by the lungs and kidneys. Buffers, especially proteins, HCO_3^{2-} , and ammonia have a very large capacity to absorb or release H^+ as needed to resist a change in pH. They can act within fractions of a second. The lungs can rid the body of excess acid very rapidly (seconds to minutes) through the conversion of HCO_3^- into CO_2 , which is then exhaled. It is rapid but has limited capacity in the face of a significant acid challenge. The kidneys can rid the body of both acid and base. The renal capacity is large but slow (minutes to hours). The cells of the PCT actively secrete H^+ into the forming urine as Na^+ is reabsorbed. The body rids itself of excess H^+ and raises blood pH. In the collecting ducts, the apical surfaces of intercalated cells have proton pumps that actively secrete H^+ into the luminal, forming urine to remove it from the body.

As hydrogen ions are pumped into the forming urine, it is buffered by bicarbonate (HCO_3^-), H_2PO_4^- (dihydrogen phosphate ion), or ammonia (forming NH_4^+ , ammonium ion). Urine pH typically varies in a normal range from 4.5 to 8.0.

Regulation of Nitrogen Wastes

Nitrogen wastes are produced by the breakdown of proteins during normal metabolism. Proteins are broken down into amino acids, which in turn are deaminated by having their nitrogen groups removed. Deamination converts the amino (NH_2) groups into ammonia (NH_3), ammonium ion (NH_4^+), urea, or uric acid ([\[link\]](#)). Ammonia is extremely toxic, so most of it is very rapidly converted into urea in the liver. Human urinary wastes typically contain primarily urea with small amounts of ammonium and very little uric acid.

Nitrogen Wastes



Elimination of Drugs and Hormones

Water-soluble drugs may be excreted in the urine and are influenced by one or all of the following processes: glomerular filtration, tubular secretion, or tubular reabsorption. Drugs that are structurally small can be filtered by the glomerulus with the filtrate. Large drug molecules such as heparin or those that are bound to plasma proteins cannot be filtered and are not readily eliminated. Some drugs can be eliminated by carrier proteins that enable secretion of the drug into the tubule lumen. There are specific carriers that eliminate basic (such as dopamine or histamine) or acidic drugs (such as

penicillin or indomethacin). As is the case with other substances, drugs may be both filtered and reabsorbed passively along a concentration gradient.

Chapter Review

The major hormones regulating body fluids are ADH, aldosterone and ANH. Progesterone is similar in structure to aldosterone and can bind to and weakly stimulate aldosterone receptors, providing a similar but diminished response. Blood pressure is a reflection of blood volume and is monitored by baroreceptors in the aortic arch and carotid sinuses. When blood pressure increases, more action potentials are sent to the central nervous system, resulting in greater vasodilation, greater GFR, and more water lost in the urine. ANH is released by the cardiomyocytes when blood pressure increases, causing Na^+ and water loss. ADH at high levels causes vasoconstriction in addition to its action on the collecting ducts to recover more water. Diuretics increase urine volume. Mechanisms for controlling Na^+ concentration in the blood include the renin–angiotensin–aldosterone system and ADH. When Na^+ is retained, K^+ is excreted; when Na^+ is lost, K^+ is retained. When circulating Ca^{++} decreases, PTH stimulates the reabsorption of Ca^{++} and inhibits reabsorption of HPO_4^{2-} . pH is regulated through buffers, expiration of CO_2 , and excretion of acid or base by the kidneys. The breakdown of amino acids produces ammonia. Most ammonia is converted into less-toxic urea in the liver and excreted in the urine. Regulation of drugs is by glomerular filtration, tubular secretion, and tubular reabsorption.

Review Questions

Exercise:

Problem: Which of these beverages does *not* have a diuretic effect?

- a. tea
- b. coffee
- c. alcohol
- d. milk

Solution:

D

Exercise:

Problem:

Progesterone can bind to receptors for which hormone that, when released, activates water retention?

- a. aldosterone
- b. ADH
- c. PTH
- d. ANH

Solution:

A

Exercise:

Problem: Renin is released in response to _____.

- a. increased blood pressure
- b. decreased blood pressure
- c. ACE
- d. diuretics

Solution:

B

Critical Thinking Questions

Exercise:

Problem: Why is ADH also called vasopressin?

Solution:

When first discovered, it was named for its known activity—vasoconstriction.

Exercise:

Problem: How can glucose be a diuretic?

Solution:

In cases of diabetes mellitus, there is more glucose present than the kidney can recover and the excess glucose is lost in the urine. It possesses osmotic character so that it attracts water to the forming urine.

Glossary

diuretic

compound that increases urine output, leading to decreased water conservation

The Urinary System and Homeostasis

By the end of this section, you will be able to:

- Describe the role of the kidneys in vitamin D activation
- Describe the role of the kidneys in regulating erythropoiesis
- Provide specific examples to demonstrate how the urinary system responds to maintain homeostasis in the body
- Explain how the urinary system relates to other body systems in maintaining homeostasis
- Predict factors or situations affecting the urinary system that could disrupt homeostasis
- Predict the types of problems that would occur in the body if the urinary system could not maintain homeostasis

All systems of the body are interrelated. A change in one system may affect all other systems in the body, with mild to devastating effects. A failure of urinary continence can be embarrassing and inconvenient, but is not life threatening. The loss of other urinary functions may prove fatal. A failure to synthesize vitamin D is one such example.

Vitamin D Synthesis

In order for vitamin D to become active, it must undergo a hydroxylation reaction in the kidney, that is, an –OH group must be added to calcidiol to make calcitriol (1,25-dihydroxycholecalciferol). Activated vitamin D is important for absorption of Ca^{++} in the digestive tract, its reabsorption in the kidney, and the maintenance of normal serum concentrations of Ca^{++} and phosphate. Calcium is vitally important in bone health, muscle contraction, hormone secretion, and neurotransmitter release. Inadequate Ca^{++} leads to disorders like osteoporosis and **osteomalacia** in adults and rickets in children. Deficits may also result in problems with cell proliferation, neuromuscular function, blood clotting, and the inflammatory response. Recent research has confirmed that vitamin D receptors are present in most, if not all, cells of the body, reflecting the systemic importance of vitamin D. Many scientists have suggested it be referred to as a hormone rather than a vitamin.

Erythropoiesis

EPO is a 193-amino acid protein that stimulates the formation of red blood cells in the bone marrow. The kidney produces 85 percent of circulating EPO; the liver, the remainder. If you move to a higher altitude, the partial pressure of oxygen is lower, meaning there is less pressure to push oxygen across the alveolar membrane and into the red blood cell. One way the body compensates is to manufacture more red blood cells by increasing EPO production. If you start an aerobic exercise program, your tissues will need more oxygen to cope, and the kidney will respond with more EPO. If erythrocytes are lost due to severe or prolonged bleeding, or under produced due to disease or severe malnutrition, the kidneys come to the rescue by producing more EPO. Renal failure (loss of EPO production) is associated with anemia, which makes it difficult for the body to cope with increased oxygen demands or to supply oxygen adequately even under normal conditions. Anemia diminishes performance and can be life threatening.

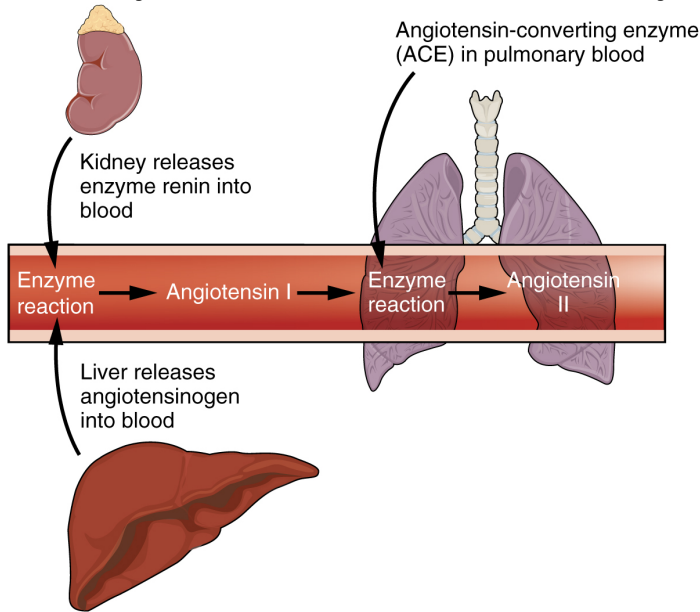
Blood Pressure Regulation

Due to osmosis, water follows where Na^+ leads. Much of the water the kidneys recover from the forming urine follows the reabsorption of Na^+ . ADH stimulation of aquaporin channels allows for regulation of water recovery in the collecting ducts. Normally, all of the glucose is recovered, but loss of glucose control (diabetes mellitus) may result in an osmotic diuresis severe enough to produce severe dehydration and death. A loss of renal function means a loss of effective vascular volume control, leading to hypotension (low blood pressure) or hypertension (high blood pressure), which can lead to stroke, heart attack, and aneurysm formation.

The kidneys cooperate with the lungs, liver, and adrenal cortex through the renin–angiotensin–aldosterone system (see [\[link\]](#)). The liver synthesizes and secretes the inactive precursor angiotensinogen. When the blood pressure is low, the kidney synthesizes and releases renin. Renin converts angiotensinogen into angiotensin I, and ACE produced in the lung converts angiotensin I into biologically active angiotensin II ([\[link\]](#)). The immediate and short-term effect of angiotensin II is to raise blood pressure by causing

widespread vasoconstriction. angiotensin II also stimulates the adrenal cortex to release the steroid hormone aldosterone, which results in renal reabsorption of Na^+ and its associated osmotic recovery of water. The reabsorption of Na^+ helps to raise and maintain blood pressure over a longer term.

The Enzyme Renin Converts the Pro-enzyme Angiotensin



Regulation of Osmolarity

Blood pressure and osmolarity are regulated in a similar fashion. Severe hypo-osmolarity can cause problems like lysis (rupture) of blood cells or widespread edema, which is due to a solute imbalance. Inadequate solute concentration (such as protein) in the plasma results in water moving toward an area of greater solute concentration, in this case, the interstitial space and cell cytoplasm. If the kidney glomeruli are damaged by an autoimmune illness, large quantities of protein may be lost in the urine. The resultant drop in serum osmolarity leads to widespread edema that, if severe, may lead to damaging or fatal brain swelling. Severe hypertonic conditions may arise with severe dehydration from lack of water intake, severe vomiting, or uncontrolled diarrhea. When the kidney is unable to recover sufficient water from the forming urine, the consequences may be severe (lethargy, confusion, muscle cramps, and finally, death) .

Recovery of Electrolytes

Sodium, calcium, and potassium must be closely regulated. The role of Na^+ and Ca^{++} homeostasis has been discussed at length. Failure of K^+ regulation can have serious consequences on nerve conduction, skeletal muscle function, and most significantly, on cardiac muscle contraction and rhythm.

pH Regulation

Recall that enzymes lose their three-dimensional conformation and, therefore, their function if the pH is too acidic or basic. This loss of conformation may be a consequence of the breaking of hydrogen bonds. Move the pH away from the optimum for a specific enzyme and you may severely hamper its function throughout the body, including hormone binding, central nervous system signaling, or myocardial contraction. Proper kidney function is essential for pH homeostasis.

Note:

Everyday Connection

Stem Cells and Repair of Kidney Damage

Stem cells are unspecialized cells that can reproduce themselves via cell division, sometimes after years of inactivity. Under certain conditions, they may differentiate into tissue-specific or organ-specific cells with special functions. In some cases, stem cells may continually divide to produce a mature cell and to replace themselves. Stem cell therapy has an enormous potential to improve the quality of life or save the lives of people suffering from debilitating or life-threatening diseases. There have been several studies in animals, but since stem cell therapy is still in its infancy, there have been limited experiments in humans.

Acute kidney injury can be caused by a number of factors, including transplants and other surgeries. It affects 7–10 percent of all hospitalized patients, resulting in the deaths of 35–40 percent of inpatients. In limited studies using mesenchymal stem cells, there have been fewer instances of kidney damage after surgery, the length of hospital stays has been reduced, and there have been fewer readmissions after release.

How do these stem cells work to protect or repair the kidney? Scientists are unsure at this point, but some evidence has shown that these stem cells release several growth factors in endocrine and paracrine ways. As further studies are conducted to assess the safety and effectiveness of stem cell therapy, we will move closer to a day when kidney injury is rare, and curative treatments are routine.

Chapter Review

The effects of failure of parts of the urinary system may range from inconvenient (incontinence) to fatal (loss of filtration and many others). The kidneys catalyze the final reaction in the synthesis of active vitamin D that in turn helps regulate Ca^{++} . The kidney hormone EPO stimulates erythrocyte development and promotes adequate O_2 transport. The kidneys help regulate blood pressure through Na^+ and water retention and loss. The kidneys work with the adrenal cortex, lungs, and liver in the renin–angiotensin–aldosterone system to regulate blood pressure. They regulate osmolarity of the blood by regulating both solutes and water. Three electrolytes are more closely regulated than others: Na^+ , Ca^{++} , and K^+ . The kidneys share pH regulation with the lungs and plasma buffers, so that proteins can preserve their three-dimensional conformation and thus their function.

Review Questions

Exercise:

Problem:

Which step in vitamin D production does the kidney perform?

- a. converts cholecalciferol into calcidiol
- b. converts calcidiol into calcitriol
- c. stores vitamin D
- d. none of these

Solution:

B

Exercise:

Problem:

Which hormone does the kidney produce that stimulates red blood cell production?

- a. thrombopoeitin
- b. vitamin D
- c. EPO
- d. renin

Solution:

C

Exercise:

Problem:

If there were no aquaporin channels in the collecting duct, _____.

- a. you would develop systemic edema
- b. you would retain excess Na^+
- c. you would lose vitamins and electrolytes
- d. you would suffer severe dehydration

Solution:

D

Critical Thinking Questions

Exercise:

Problem:How does lack of protein in the blood cause edema?

Solution:

Protein has osmotic properties. If there is not enough protein in the blood, water will be attracted to the interstitial space and the cell cytoplasm resulting in tissue edema.

Exercise:

Problem:

Which three electrolytes are most closely regulated by the kidney?

Solution:

The three electrolytes are most closely regulated by the kidney are calcium, sodium, and potassium.

References

Bagul A, Frost JH, Drage M. Stem cells and their role in renal ischaemia reperfusion injury. Am J Nephrol [Internet]. 2013 [cited 2013 Apr 15]; 37(1):16–29. Available from: <http://www.karger.com/Article/FullText/345731>

Glossary

osteomalacia

softening of bones due to a lack of mineralization with calcium and phosphate; most often due to lack of vitamin D; in children, osteomalacia is termed rickets; not to be confused with osteoporosis

Introduction

class="introduction"

Robotic Arms Playing Foosball

As the neural circuitry of the nervous system has become more fully understood and robotics more sophisticated, it is now possible to integrate technology with the body and restore abilities following traumatic events. At some point in the future, will this type of technology lead to the ability to augment our nervous systems? (credit: U.S. Army/Wikimedia Commons)

**Note:****Chapter Objectives**

After studying this chapter, you will be able to:

- Name the major divisions of the nervous system, both anatomical and functional
- Describe the functional and structural differences between gray matter and white matter structures
- Name the parts of the multipolar neuron in order of polarity
- List the types of glial cells and assign each to the proper division of the nervous system, along with their function(s)
- Distinguish the major functions of the nervous system: sensation, integration, and response

- Describe the components of the membrane that establish the resting membrane potential
- Describe the changes that occur to the membrane that result in the action potential
- Explain the differences between types of graded potentials
- Categorize the major neurotransmitters by chemical type and effect

The nervous system is a very complex organ system. In Peter D. Kramer's book *Listening to Prozac*, a pharmaceutical researcher is quoted as saying, "If the human brain were simple enough for us to understand, we would be too simple to understand it" (1994). That quote is from the early 1990s; in the two decades since, progress has continued at an amazing rate within the scientific disciplines of neuroscience. It is an interesting conundrum to consider that the complexity of the nervous system may be too complex for it (that is, for us) to completely unravel. But our current level of understanding is probably nowhere close to that limit.

One easy way to begin to understand the structure of the nervous system is to start with the large divisions and work through to a more in-depth understanding. In other chapters, the finer details of the nervous system will be explained, but first looking at an overview of the system will allow you to begin to understand how its parts work together. The focus of this chapter is on nervous (neural) tissue, both its structure and its function. But before you learn about that, you will see a big picture of the system—actually, a few big pictures.

Basic Structure and Function of the Nervous System

By the end of this section, you will be able to:

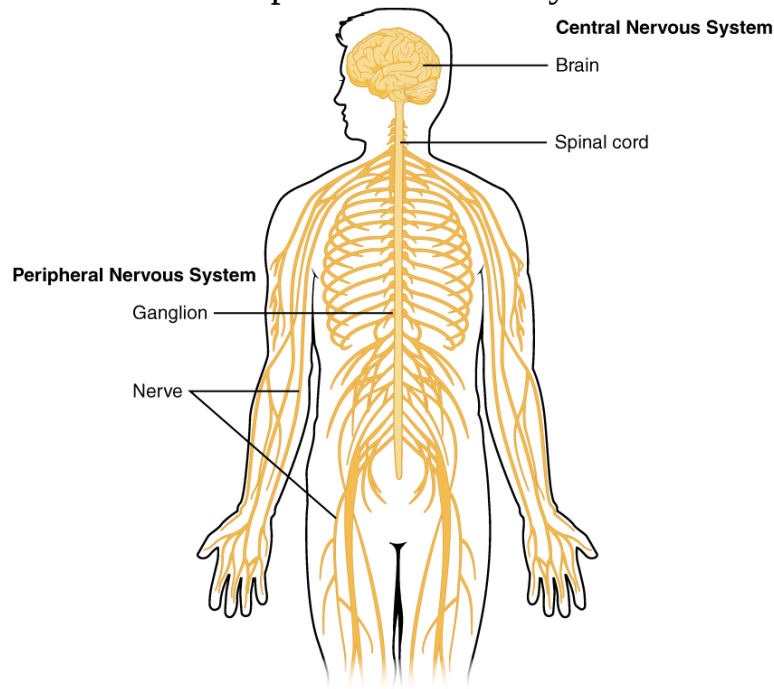
- Identify the anatomical and functional divisions of the nervous system
- Relate the functional and structural differences between gray matter and white matter structures of the nervous system to the structure of neurons
- List the basic functions of the nervous system

The picture you have in your mind of the nervous system probably includes the **brain**, the nervous tissue contained within the cranium, and the **spinal cord**, the extension of nervous tissue within the vertebral column. That suggests it is made of two organs—and you may not even think of the spinal cord as an organ—but the nervous system is a very complex structure. Within the brain, many different and separate regions are responsible for many different and separate functions. It is as if the nervous system is composed of many organs that all look similar and can only be differentiated using tools such as the microscope or electrophysiology. In comparison, it is easy to see that the stomach is different than the esophagus or the liver, so you can imagine the digestive system as a collection of specific organs.

The Central and Peripheral Nervous Systems

The nervous system can be divided into two major regions: the central and peripheral nervous systems. The **central nervous system (CNS)** is the brain and spinal cord, and the **peripheral nervous system (PNS)** is everything else ([\[link\]](#)). The brain is contained within the cranial cavity of the skull, and the spinal cord is contained within the vertebral cavity of the vertebral column. It is a bit of an oversimplification to say that the CNS is what is inside these two cavities and the peripheral nervous system is outside of them, but that is one way to start to think about it. In actuality, there are some elements of the peripheral nervous system that are within the cranial or vertebral cavities. The peripheral nervous system is so named because it is on the periphery—meaning beyond the brain and spinal cord. Depending on different aspects of the nervous system, the dividing line between central and peripheral is not necessarily universal.

Central and Peripheral Nervous System



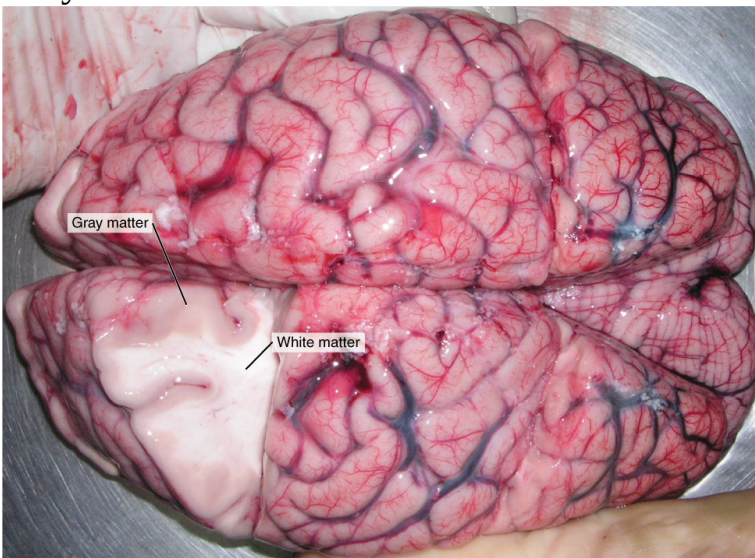
The structures of the PNS are referred to as ganglia and nerves, which can be seen as distinct structures. The equivalent structures in the CNS are not obvious from this overall perspective and are best examined in prepared tissue under the microscope.

Nervous tissue, present in both the CNS and PNS, contains two basic types of cells: neurons and glial cells. A **glial cell** is one of a variety of cells that provide a framework of tissue that supports the neurons and their activities. The **neuron** is the more functionally important of the two, in terms of the communicative function of the nervous system. To describe the functional divisions of the nervous system, it is important to understand the structure of a neuron. Neurons are cells and therefore have a **soma**, or cell body, but they also have extensions of the cell; each extension is generally referred to as a **process**. There is one important process that every neuron has called an **axon**, which is the fiber that connects a neuron with its target. Another type

of process that branches off from the soma is the **dendrite**. Dendrites are responsible for receiving most of the input from other neurons. Looking at nervous tissue, there are regions that predominantly contain cell bodies and regions that are largely composed of just axons. These two regions within nervous system structures are often referred to as **gray matter** (the regions with many cell bodies and dendrites) or **white matter** (the regions with many axons). [\[link\]](#) demonstrates the appearance of these regions in the brain and spinal cord. The colors ascribed to these regions are what would be seen in “fresh,” or unstained, nervous tissue. Gray matter is not necessarily gray. It can be pinkish because of blood content, or even slightly tan, depending on how long the tissue has been preserved. But white matter is white because axons are insulated by a lipid-rich substance called **myelin**. Lipids can appear as white (“fatty”) material, much like the fat on a raw piece of chicken or beef. Actually, gray matter may have that color ascribed to it because next to the white matter, it is just darker—hence, gray.

The distinction between gray matter and white matter is most often applied to central nervous tissue, which has large regions that can be seen with the unaided eye. When looking at peripheral structures, often a microscope is used and the tissue is stained with artificial colors. That is not to say that central nervous tissue cannot be stained and viewed under a microscope, but unstained tissue is most likely from the CNS—for example, a frontal section of the brain or cross section of the spinal cord.

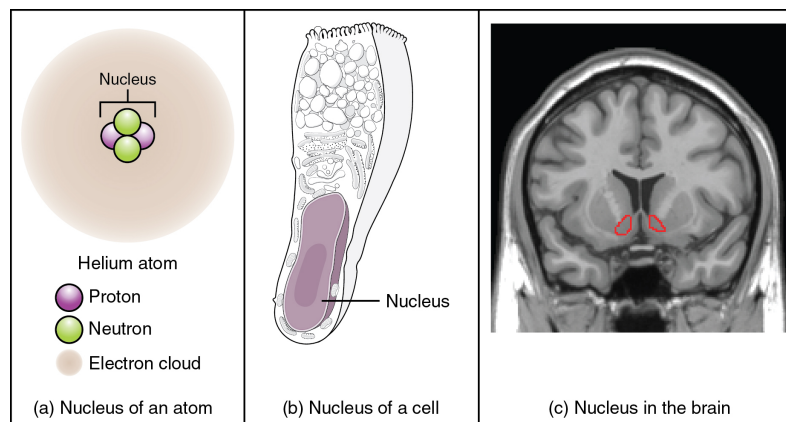
Gray Matter and White Matter



A brain removed during an autopsy, with a partial section removed, shows white matter surrounded by gray matter. Gray matter makes up the outer cortex of the brain. (credit: modification of work by “Suseno”/Wikimedia Commons)

Regardless of the appearance of stained or unstained tissue, the cell bodies of neurons or axons can be located in discrete anatomical structures that need to be named. Those names are specific to whether the structure is central or peripheral. A localized collection of neuron cell bodies in the CNS is referred to as a **nucleus**. In the PNS, a cluster of neuron cell bodies is referred to as a **ganglion**. [\[link\]](#) indicates how the term nucleus has a few different meanings within anatomy and physiology. It is the center of an atom, where protons and neutrons are found; it is the center of a cell, where the DNA is found; and it is a center of some function in the CNS. There is also a potentially confusing use of the word ganglion (plural = ganglia) that has a historical explanation. In the central nervous system, there is a group of nuclei that are connected together and were once called the basal ganglia before “ganglion” became accepted as a description for a peripheral structure. Some sources refer to this group of nuclei as the “basal nuclei” to avoid confusion.

What Is a Nucleus?

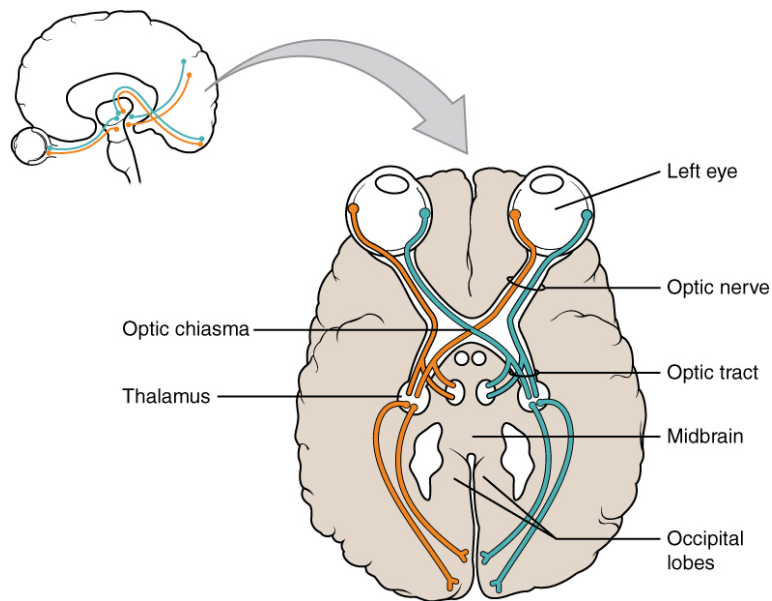


(a) The nucleus of an atom contains its

protons and neutrons. (b) The nucleus of a cell is the organelle that contains DNA. (c) A nucleus in the CNS is a localized center of function with the cell bodies of several neurons, shown here circled in red. (credit c: "Was a bee"/Wikimedia Commons)

Terminology applied to bundles of axons also differs depending on location. A bundle of axons, or fibers, found in the CNS is called a **tract** whereas the same thing in the PNS would be called a **nerve**. There is an important point to make about these terms, which is that they can both be used to refer to the same bundle of axons. When those axons are in the PNS, the term is nerve, but if they are CNS, the term is tract. The most obvious example of this is the axons that project from the retina into the brain. Those axons are called the optic nerve as they leave the eye, but when they are inside the cranium, they are referred to as the optic tract. There is a specific place where the name changes, which is the optic chiasm, but they are still the same axons ([\[link\]](#)). A similar situation outside of science can be described for some roads. Imagine a road called "Broad Street" in a town called "Anyville." The road leaves Anyville and goes to the next town over, called "Hometown." When the road crosses the line between the two towns and is in Hometown, its name changes to "Main Street." That is the idea behind the naming of the retinal axons. In the PNS, they are called the optic nerve, and in the CNS, they are the optic tract. [\[link\]](#) helps to clarify which of these terms apply to the central or peripheral nervous systems.

Optic Nerve Versus Optic Tract



This drawing of the connections of the eye to the brain shows the optic nerve extending from the eye to the chiasm, where the structure continues as the optic tract. The same axons extend from the eye to the brain through these two bundles of fibers, but the chiasm represents the border between peripheral and central.

Note:



In 2003, the Nobel Prize in Physiology or Medicine was awarded to Paul C. Lauterbur and Sir Peter Mansfield for discoveries related to magnetic

resonance imaging (MRI). This is a tool to see the structures of the body (not just the nervous system) that depends on magnetic fields associated with certain atomic nuclei. The utility of this technique in the nervous system is that fat tissue and water appear as different shades between black and white. Because white matter is fatty (from myelin) and gray matter is not, they can be easily distinguished in MRI images. Visit the Nobel Prize [web site](#) to play an interactive game that demonstrates the use of this technology and compares it with other types of imaging technologies. Also, the results from an MRI session are compared with images obtained from X-ray or computed tomography. How do the imaging techniques shown in this game indicate the separation of white and gray matter compared with the freshly dissected tissue shown earlier?

| Structures of the CNS and PNS | | |
|---|------------|------------|
| | CNS | PNS |
| Group of Neuron Cell Bodies (i.e., gray matter) | Nucleus | Ganglion |
| Bundle of Axons (i.e., white matter) | Tract | Nerve |

Functional Divisions of the Nervous System

The nervous system can also be divided on the basis of its functions, but anatomical divisions and functional divisions are different. The CNS and the PNS both contribute to the same functions, but those functions can be attributed to different regions of the brain (such as the cerebral cortex or the hypothalamus) or to different ganglia in the periphery. The problem with trying to fit functional differences into anatomical divisions is that sometimes the same structure can be part of several functions. For example,

the optic nerve carries signals from the retina that are either used for the conscious perception of visual stimuli, which takes place in the cerebral cortex, or for the reflexive responses of smooth muscle tissue that are processed through the hypothalamus.

There are two ways to consider how the nervous system is divided functionally. First, the basic functions of the nervous system are sensation, integration, and response. Secondly, control of the body can be somatic or autonomic—divisions that are largely defined by the structures that are involved in the response. There is also a region of the peripheral nervous system that is called the enteric nervous system that is responsible for a specific set of the functions within the realm of autonomic control related to gastrointestinal functions.

Basic Functions

The nervous system is involved in receiving information about the environment around us (sensation) and generating responses to that information (motor responses). The nervous system can be divided into regions that are responsible for **sensation** (sensory functions) and for the **response** (motor functions). But there is a third function that needs to be included. Sensory input needs to be integrated with other sensations, as well as with memories, emotional state, or learning (cognition). Some regions of the nervous system are termed **integration** or association areas. The process of integration combines sensory perceptions and higher cognitive functions such as memories, learning, and emotion to produce a response.

Sensation. The first major function of the nervous system is sensation—receiving information about the environment to gain input about what is happening outside the body (or, sometimes, within the body). The sensory functions of the nervous system register the presence of a change from homeostasis or a particular event in the environment, known as a **stimulus**. The senses we think of most are the “big five”: taste, smell, touch, sight, and hearing. The stimuli for taste and smell are both chemical substances (molecules, compounds, ions, etc.), touch is physical or mechanical stimuli that interact with the skin, sight is light stimuli, and hearing is the

perception of sound, which is a physical stimulus similar to some aspects of touch. There are actually more senses than just those, but that list represents the major senses. Those five are all senses that receive stimuli from the outside world, and of which there is conscious perception. Additional sensory stimuli might be from the internal environment (inside the body), such as the stretch of an organ wall or the concentration of certain ions in the blood.

Response. The nervous system produces a response on the basis of the stimuli perceived by sensory structures. An obvious response would be the movement of muscles, such as withdrawing a hand from a hot stove, but there are broader uses of the term. The nervous system can cause the contraction of all three types of muscle tissue. For example, skeletal muscle contracts to move the skeleton, cardiac muscle is influenced as heart rate increases during exercise, and smooth muscle contracts as the digestive system moves food along the digestive tract. Responses also include the neural control of glands in the body as well, such as the production and secretion of sweat by the eccrine and merocrine sweat glands found in the skin to lower body temperature.

Responses can be divided into those that are voluntary or conscious (contraction of skeletal muscle) and those that are involuntary (contraction of smooth muscles, regulation of cardiac muscle, activation of glands). Voluntary responses are governed by the somatic nervous system and involuntary responses are governed by the autonomic nervous system, which are discussed in the next section.

Integration. Stimuli that are received by sensory structures are communicated to the nervous system where that information is processed. This is called integration. Stimuli are compared with, or integrated with, other stimuli, memories of previous stimuli, or the state of a person at a particular time. This leads to the specific response that will be generated. Seeing a baseball pitched to a batter will not automatically cause the batter to swing. The trajectory of the ball and its speed will need to be considered. Maybe the count is three balls and one strike, and the batter wants to let this pitch go by in the hope of getting a walk to first base. Or maybe the batter's team is so far ahead, it would be fun to just swing away.

Controlling the Body

The nervous system can be divided into two parts mostly on the basis of a functional difference in responses. The **somatic nervous system (SNS)** is responsible for conscious perception and voluntary motor responses.

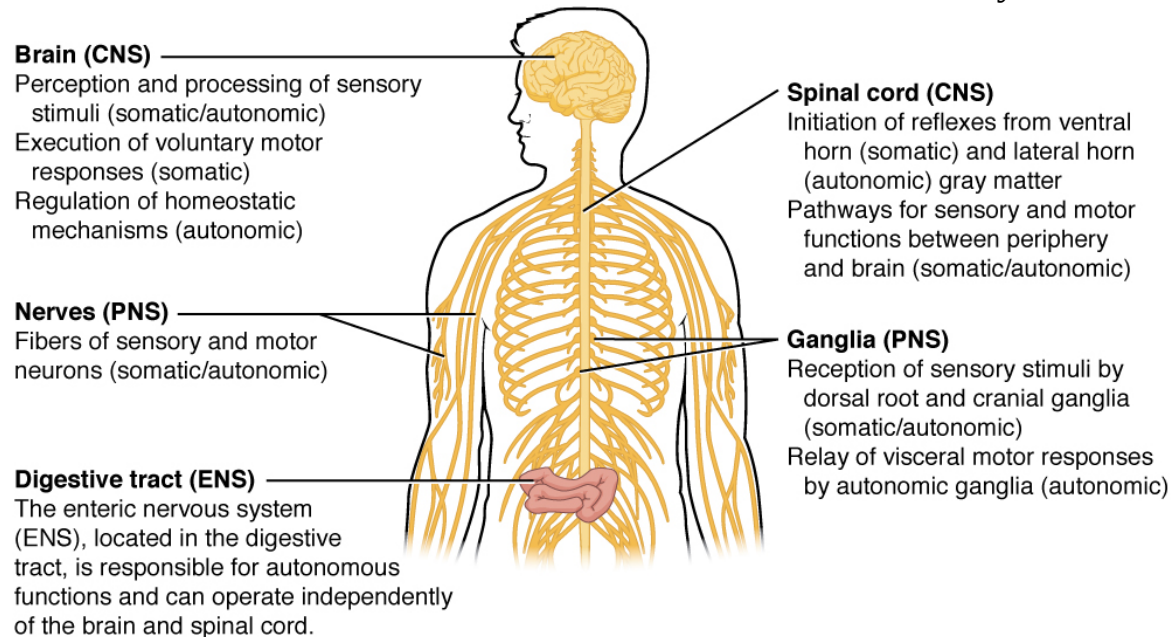
Voluntary motor response means the contraction of skeletal muscle, but those contractions are not always voluntary in the sense that you have to want to perform them. Some somatic motor responses are reflexes, and often happen without a conscious decision to perform them. If your friend jumps out from behind a corner and yells “Boo!” you will be startled and you might scream or leap back. You didn’t decide to do that, and you may not have wanted to give your friend a reason to laugh at your expense, but it is a reflex involving skeletal muscle contractions. Other motor responses become automatic (in other words, unconscious) as a person learns motor skills (referred to as “habit learning” or “procedural memory”).

The **autonomic nervous system (ANS)** is responsible for involuntary control of the body, usually for the sake of homeostasis (regulation of the internal environment). Sensory input for autonomic functions can be from sensory structures tuned to external or internal environmental stimuli. The motor output extends to smooth and cardiac muscle as well as glandular tissue. The role of the autonomic system is to regulate the organ systems of the body, which usually means to control homeostasis. Sweat glands, for example, are controlled by the autonomic system. When you are hot, sweating helps cool your body down. That is a homeostatic mechanism. But when you are nervous, you might start sweating also. That is not homeostatic, it is the physiological response to an emotional state.

There is another division of the nervous system that describes functional responses. The **enteric nervous system (ENS)** is responsible for controlling the smooth muscle and glandular tissue in your digestive system. It is a large part of the PNS, and is not dependent on the CNS. It is sometimes valid, however, to consider the enteric system to be a part of the autonomic system because the neural structures that make up the enteric system are a component of the autonomic output that regulates digestion. There are some differences between the two, but for our purposes here there

will be a good bit of overlap. See [\[link\]](#) for examples of where these divisions of the nervous system can be found.

Somatic, Autonomic, and Enteric Structures of the Nervous System



Somatic structures include the spinal nerves, both motor and sensory fibers, as well as the sensory ganglia (posterior root ganglia and cranial nerve ganglia). Autonomic structures are found in the nerves also, but include the sympathetic and parasympathetic ganglia. The enteric nervous system includes the nervous tissue within the organs of the digestive tract.

Note:



Visit this [site](#) to read about a woman that notices that her daughter is having trouble walking up the stairs. This leads to the discovery of a hereditary condition that affects the brain and spinal cord. The electromyography and MRI tests indicated deficiencies in the spinal cord and cerebellum, both of which are responsible for controlling coordinated movements. To what functional division of the nervous system would these structures belong?

Note:

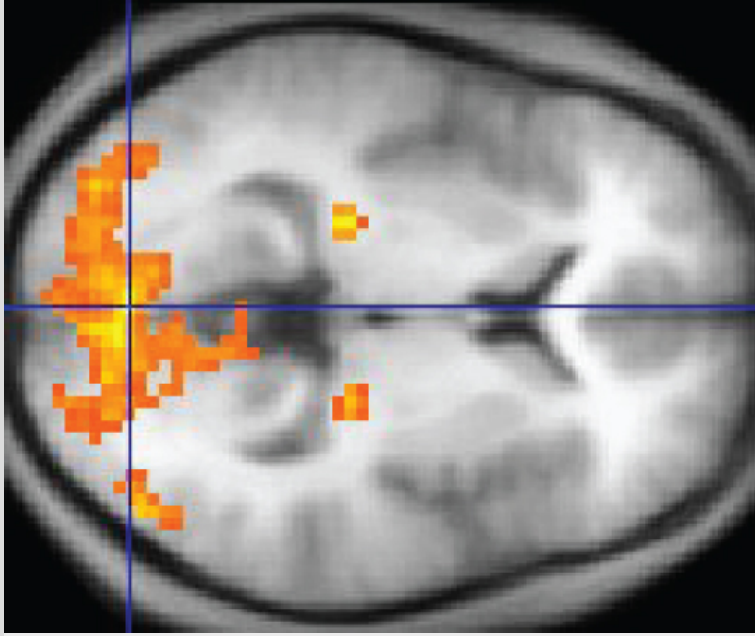
Everyday Connection

How Much of Your Brain Do You Use?

Have you ever heard the claim that humans only use 10 percent of their brains? Maybe you have seen an advertisement on a website saying that there is a secret to unlocking the full potential of your mind—as if there were 90 percent of your brain sitting idle, just waiting for you to use it. If you see an ad like that, don't click. It isn't true.

An easy way to see how much of the brain a person uses is to take measurements of brain activity while performing a task. An example of this kind of measurement is functional magnetic resonance imaging (fMRI), which generates a map of the most active areas and can be generated and presented in three dimensions ([\[link\]](#)). This procedure is different from the standard MRI technique because it is measuring changes in the tissue in time with an experimental condition or event.

fMRI



This fMRI shows activation of the visual cortex in response to visual stimuli.
(credit: "Superborsuk"/Wikimedia Commons)

The underlying assumption is that active nervous tissue will have greater blood flow. By having the subject perform a visual task, activity all over the brain can be measured. Consider this possible experiment: the subject is told to look at a screen with a black dot in the middle (a fixation point). A photograph of a face is projected on the screen away from the center. The subject has to look at the photograph and decipher what it is. The subject has been instructed to push a button if the photograph is of someone they recognize. The photograph might be of a celebrity, so the subject would press the button, or it might be of a random person unknown to the subject, so the subject would not press the button.

In this task, visual sensory areas would be active, integrating areas would be active, motor areas responsible for moving the eyes would be active, and motor areas for pressing the button with a finger would be active. Those areas are distributed all around the brain and the fMRI images would show activity in more than just 10 percent of the brain (some evidence suggests that about 80 percent of the brain is using energy—

based on blood flow to the tissue—during well-defined tasks similar to the one suggested above). This task does not even include all of the functions the brain performs. There is no language response, the body is mostly lying still in the MRI machine, and it does not consider the autonomic functions that would be ongoing in the background.

Chapter Review

The nervous system can be separated into divisions on the basis of anatomy and physiology. The anatomical divisions are the central and peripheral nervous systems. The CNS is the brain and spinal cord. The PNS is everything else. Functionally, the nervous system can be divided into those regions that are responsible for sensation, those that are responsible for integration, and those that are responsible for generating responses. All of these functional areas are found in both the central and peripheral anatomy.

Considering the anatomical regions of the nervous system, there are specific names for the structures within each division. A localized collection of neuron cell bodies is referred to as a nucleus in the CNS and as a ganglion in the PNS. A bundle of axons is referred to as a tract in the CNS and as a nerve in the PNS. Whereas nuclei and ganglia are specifically in the central or peripheral divisions, axons can cross the boundary between the two. A single axon can be part of a nerve and a tract. The name for that specific structure depends on its location.

Nervous tissue can also be described as gray matter and white matter on the basis of its appearance in unstained tissue. These descriptions are more often used in the CNS. Gray matter is where nuclei are found and white matter is where tracts are found. In the PNS, ganglia are basically gray matter and nerves are white matter.

The nervous system can also be divided on the basis of how it controls the body. The somatic nervous system (SNS) is responsible for functions that result in moving skeletal muscles. Any sensory or integrative functions that result in the movement of skeletal muscle would be considered somatic. The autonomic nervous system (ANS) is responsible for functions that

affect cardiac or smooth muscle tissue, or that cause glands to produce their secretions. Autonomic functions are distributed between central and peripheral regions of the nervous system. The sensations that lead to autonomic functions can be the same sensations that are part of initiating somatic responses. Somatic and autonomic integrative functions may overlap as well.

A special division of the nervous system is the enteric nervous system, which is responsible for controlling the digestive organs. Parts of the autonomic nervous system overlap with the enteric nervous system. The enteric nervous system is exclusively found in the periphery because it is the nervous tissue in the organs of the digestive system.

Interactive Link Questions

Exercise:

Problem:

In 2003, the Nobel Prize in Physiology or Medicine was awarded to Paul C. Lauterbur and Sir Peter Mansfield for discoveries related to magnetic resonance imaging (MRI). This is a tool to see the structures of the body (not just the nervous system) that depends on magnetic fields associated with certain atomic nuclei. The utility of this technique in the nervous system is that fat tissue and water appear as different shades between black and white. Because white matter is fatty (from myelin) and gray matter is not, they can be easily distinguished in MRI images. Visit the Nobel Prize [website](#) to play an interactive game that demonstrates the use of this technology and compares it with other types of imaging technologies. Also, the results from an MRI session are compared with images obtained from x-ray or computed tomography. How do the imaging techniques shown in this game indicate the separation of white and gray matter compared with the freshly dissected tissue shown earlier?

Solution:

MRI uses the relative amount of water in tissue to distinguish different areas, so gray and white matter in the nervous system can be seen clearly in these images.

Exercise:

Problem:

Visit this [site](#) to read about a woman that notices that her daughter is having trouble walking up the stairs. This leads to the discovery of a hereditary condition that affects the brain and spinal cord. The electromyography and MRI tests indicated deficiencies in the spinal cord and cerebellum, both of which are responsible for controlling coordinated movements. To what functional division of the nervous system would these structures belong?

Solution:

They are part of the somatic nervous system, which is responsible for voluntary movements such as walking or climbing the stairs.

Review Questions

Exercise:

Problem:

Which of the following cavities contains a component of the central nervous system?

- a. abdominal
- b. pelvic
- c. cranial
- d. thoracic

Solution:

C

Exercise:

Problem:

Which structure predominates in the white matter of the brain?

- a. myelinated axons
- b. neuronal cell bodies
- c. ganglia of the parasympathetic nerves
- d. bundles of dendrites from the enteric nervous system

Solution:

A

Exercise:

Problem:

Which part of a neuron transmits an electrical signal to a target cell?

- a. dendrites
- b. soma
- c. cell body
- d. axon

Solution:

D

Exercise:

Problem:

Which term describes a bundle of axons in the peripheral nervous system?

- a. nucleus
- b. ganglion

- c. tract
- d. nerve

Solution:

D

Exercise:

Problem:

Which functional division of the nervous system would be responsible for the physiological changes seen during exercise (e.g., increased heart rate and sweating)?

- a. somatic
- b. autonomic
- c. enteric
- d. central

Solution:

B

Critical Thinking Questions

Exercise:

Problem:

What responses are generated by the nervous system when you run on a treadmill? Include an example of each type of tissue that is under nervous system control.

Solution:

Running on a treadmill involves contraction of the skeletal muscles in the legs, increase in contraction of the cardiac muscle of the heart, and the production and secretion of sweat in the skin to stay cool.

Exercise:

Problem:

When eating food, what anatomical and functional divisions of the nervous system are involved in the perceptual experience?

Solution:

The sensation of taste associated with eating is sensed by nerves in the periphery that are involved in sensory and somatic functions.

References

Kramer, PD. Listening to prozac. 1st ed. New York (NY): Penguin Books; 1993.

Glossary

autonomic nervous system (ANS)

functional division of the nervous system that is responsible for homeostatic reflexes that coordinate control of cardiac and smooth muscle, as well as glandular tissue

axon

single process of the neuron that carries an electrical signal (action potential) away from the cell body toward a target cell

brain

the large organ of the central nervous system composed of white and gray matter, contained within the cranium and continuous with the spinal cord

central nervous system (CNS)

anatomical division of the nervous system located within the cranial and vertebral cavities, namely the brain and spinal cord

dendrite

one of many branchlike processes that extends from the neuron cell body and functions as a contact for incoming signals (synapses) from other neurons or sensory cells

enteric nervous system (ENS)

neural tissue associated with the digestive system that is responsible for nervous control through autonomic connections

ganglion

localized collection of neuron cell bodies in the peripheral nervous system

glial cell

one of the various types of neural tissue cells responsible for maintenance of the tissue, and largely responsible for supporting neurons

gray matter

regions of the nervous system containing cell bodies of neurons with few or no myelinated axons; actually may be more pink or tan in color, but called gray in contrast to white matter

integration

nervous system function that combines sensory perceptions and higher cognitive functions (memories, learning, emotion, etc.) to produce a response

myelin

lipid-rich insulating substance surrounding the axons of many neurons, allowing for faster transmission of electrical signals

nerve

cord-like bundle of axons located in the peripheral nervous system that transmits sensory input and response output to and from the central

nervous system

neuron

neural tissue cell that is primarily responsible for generating and propagating electrical signals into, within, and out of the nervous system

nucleus

in the nervous system, a localized collection of neuron cell bodies that are functionally related; a “center” of neural function

peripheral nervous system (PNS)

anatomical division of the nervous system that is largely outside the cranial and vertebral cavities, namely all parts except the brain and spinal cord

process

in cells, an extension of a cell body; in the case of neurons, this includes the axon and dendrites

response

nervous system function that causes a target tissue (muscle or gland) to produce an event as a consequence to stimuli

sensation

nervous system function that receives information from the environment and translates it into the electrical signals of nervous tissue

soma

in neurons, that portion of the cell that contains the nucleus; the cell body, as opposed to the cell processes (axons and dendrites)

somatic nervous system (SNS)

functional division of the nervous system that is concerned with conscious perception, voluntary movement, and skeletal muscle reflexes

spinal cord

organ of the central nervous system found within the vertebral cavity and connected with the periphery through spinal nerves; mediates reflex behaviors

stimulus

an event in the external or internal environment that registers as activity in a sensory neuron

tract

bundle of axons in the central nervous system having the same function and point of origin

white matter

regions of the nervous system containing mostly myelinated axons, making the tissue appear white because of the high lipid content of myelin

Nervous Tissue

By the end of this section, you will be able to:

- Describe the basic structure of a neuron
- Identify the different types of neurons on the basis of polarity
- List the glial cells of the CNS and describe their function
- List the glial cells of the PNS and describe their function

Nervous tissue is composed of two types of cells, neurons and glial cells. Neurons are the primary type of cell that most anyone associates with the nervous system. They are responsible for the computation and communication that the nervous system provides. They are electrically active and release chemical signals to target cells. Glial cells, or glia, are known to play a supporting role for nervous tissue. Ongoing research pursues an expanded role that glial cells might play in signaling, but neurons are still considered the basis of this function. Neurons are important, but without glial support they would not be able to perform their function.

Neurons

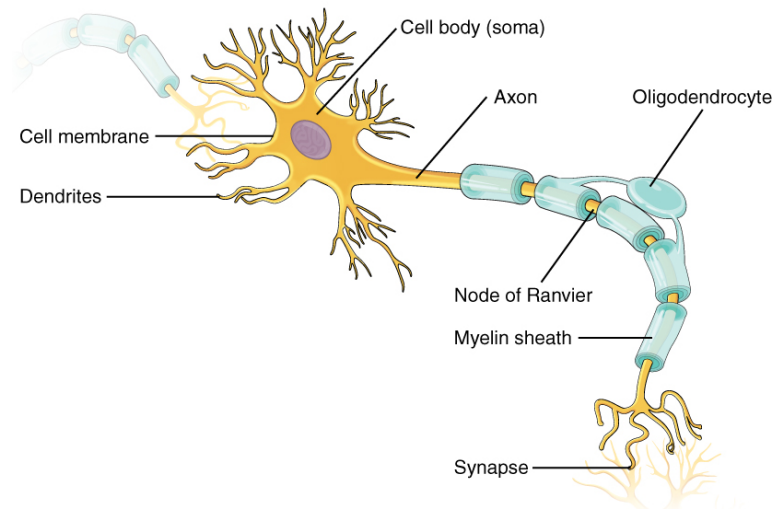
Neurons are the cells considered to be the basis of nervous tissue. They are responsible for the electrical signals that communicate information about sensations, and that produce movements in response to those stimuli, along with inducing thought processes within the brain. An important part of the function of neurons is in their structure, or shape. The three-dimensional shape of these cells makes the immense numbers of connections within the nervous system possible.

Parts of a Neuron

As you learned in the first section, the main part of a neuron is the cell body, which is also known as the soma (soma = “body”). The cell body contains the nucleus and most of the major organelles. But what makes neurons special is that they have many extensions of their cell membranes, which are generally referred to as processes. Neurons are usually described

as having one, and only one, axon—a fiber that emerges from the cell body and projects to target cells. That single axon can branch repeatedly to communicate with many target cells. It is the axon that propagates the nerve impulse, which is communicated to one or more cells. The other processes of the neuron are dendrites, which receive information from other neurons at specialized areas of contact called **synapses**. The dendrites are usually highly branched processes, providing locations for other neurons to communicate with the cell body. Information flows through a neuron from the dendrites, across the cell body, and down the axon. This gives the neuron a polarity—meaning that information flows in this one direction. [\[link\]](#) shows the relationship of these parts to one another.

Parts of a Neuron



The major parts of the neuron are labeled on a multipolar neuron from the CNS.

Where the axon emerges from the cell body, there is a special region referred to as the **axon hillock**. This is a tapering of the cell body toward the axon fiber. Within the axon hillock, the cytoplasm changes to a solution of limited components called **axoplasm**. Because the axon hillock represents the beginning of the axon, it is also referred to as the **initial segment**.

Many axons are wrapped by an insulating substance called myelin, which is actually made from glial cells. Myelin acts as insulation much like the plastic or rubber that is used to insulate electrical wires. A key difference between myelin and the insulation on a wire is that there are gaps in the myelin covering of an axon. Each gap is called a **node of Ranvier** and is important to the way that electrical signals travel down the axon. The length of the axon between each gap, which is wrapped in myelin, is referred to as an **axon segment**. At the end of the axon is the **axon terminal**, where there are usually several branches extending toward the target cell, each of which ends in an enlargement called a **synaptic end bulb**. These bulbs are what make the connection with the target cell at the synapse.

Note:



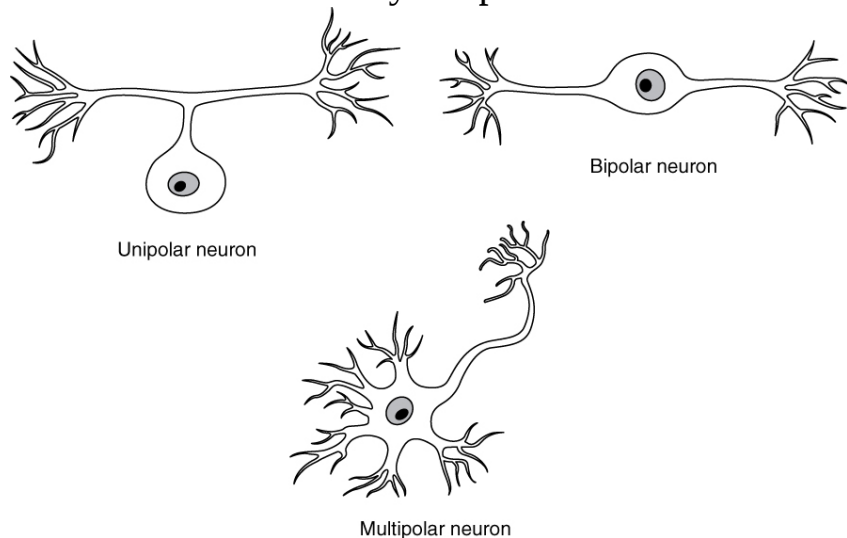
Visit this [site](#) to learn about how nervous tissue is composed of neurons and glial cells. Neurons are dynamic cells with the ability to make a vast number of connections, to respond incredibly quickly to stimuli, and to initiate movements on the basis of those stimuli. They are the focus of intense research because failures in physiology can lead to devastating illnesses. Why are neurons only found in animals? Based on what this article says about neuron function, why wouldn't they be helpful for plants or microorganisms?

Types of Neurons

There are many neurons in the nervous system—a number in the trillions. And there are many different types of neurons. They can be classified by many different criteria. The first way to classify them is by the number of

processes attached to the cell body. Using the standard model of neurons, one of these processes is the axon, and the rest are dendrites. Because information flows through the neuron from dendrites or cell bodies toward the axon, these names are based on the neuron's polarity ([\[link\]](#)).

Neuron Classification by Shape



Unipolar cells have one process that includes both the axon and dendrite. Bipolar cells have two processes, the axon and a dendrite.

Multipolar cells have more than two processes, the axon and two or more dendrites.

Unipolar cells have only one process emerging from the cell. True unipolar cells are only found in invertebrate animals, so the unipolar cells in humans are more appropriately called “pseudo-unipolar” cells. Invertebrate unipolar cells do not have dendrites. Human unipolar cells have an axon that emerges from the cell body, but it splits so that the axon can extend along a very long distance. At one end of the axon are dendrites, and at the other end, the axon forms synaptic connections with a target. Unipolar cells are exclusively sensory neurons and have two unique characteristics. First, their dendrites are receiving sensory information, sometimes directly from the stimulus itself. Secondly, the cell bodies of unipolar neurons are always found in ganglia. Sensory reception is a peripheral function (those dendrites

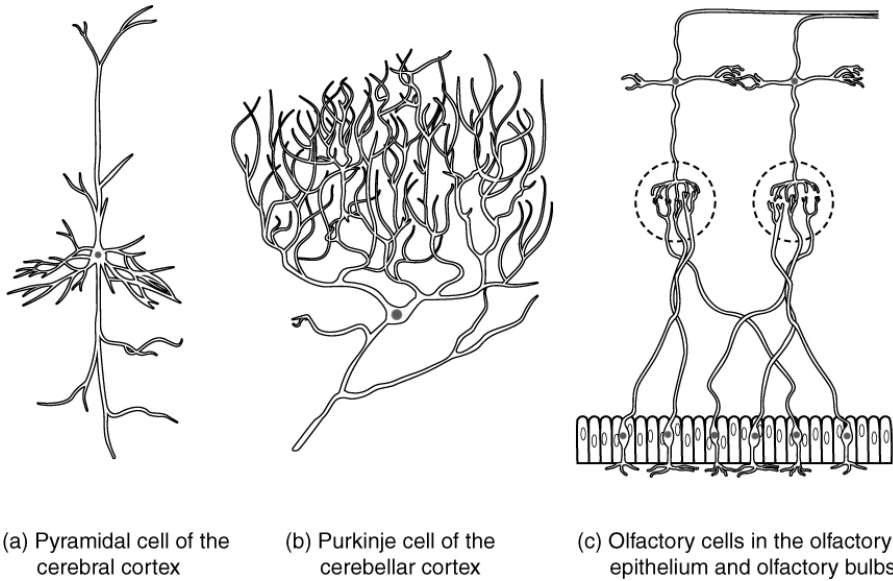
are in the periphery, perhaps in the skin) so the cell body is in the periphery, though closer to the CNS in a ganglion. The axon projects from the dendrite endings, past the cell body in a ganglion, and into the central nervous system.

Bipolar cells have two processes, which extend from each end of the cell body, opposite to each other. One is the axon and one the dendrite. Bipolar cells are not very common. They are found mainly in the olfactory epithelium (where smell stimuli are sensed), and as part of the retina.

Multipolar neurons are all of the neurons that are not unipolar or bipolar. They have one axon and two or more dendrites (usually many more). With the exception of the unipolar sensory ganglion cells, and the two specific bipolar cells mentioned above, all other neurons are multipolar. Some cutting edge research suggests that certain neurons in the CNS do not conform to the standard model of “one, and only one” axon. Some sources describe a fourth type of neuron, called an anaxonic neuron. The name suggests that it has no axon (an- = “without”), but this is not accurate. Anaxonic neurons are very small, and if you look through a microscope at the standard resolution used in histology (approximately 400X to 1000X total magnification), you will not be able to distinguish any process specifically as an axon or a dendrite. Any of those processes can function as an axon depending on the conditions at any given time. Nevertheless, even if they cannot be easily seen, and one specific process is definitively the axon, these neurons have multiple processes and are therefore multipolar.

Neurons can also be classified on the basis of where they are found, who found them, what they do, or even what chemicals they use to communicate with each other. Some neurons referred to in this section on the nervous system are named on the basis of those sorts of classifications ([\[link\]](#)). For example, a multipolar neuron that has a very important role to play in a part of the brain called the cerebellum is known as a Purkinje (commonly pronounced per-KIN-gee) cell. It is named after the anatomist who discovered it (Jan Evangelista Purkinje, 1787–1869).

Other Neuron Classifications



Three examples of neurons that are classified on the basis of other criteria. (a) The pyramidal cell is a multipolar cell with a cell body that is shaped something like a pyramid. (b) The Purkinje cell in the cerebellum was named after the scientist who originally described it. (c) Olfactory neurons are named for the functional group with which they belong.

Glial Cells

Glial cells, or neuroglia or simply glia, are the other type of cell found in nervous tissue. They are considered to be supporting cells, and many functions are directed at helping neurons complete their function for communication. The name glia comes from the Greek word that means “glue,” and was coined by the German pathologist Rudolph Virchow, who wrote in 1856: “This connective substance, which is in the brain, the spinal cord, and the special sense nerves, is a kind of glue (neuroglia) in which the nervous elements are planted.” Today, research into nervous tissue has shown that there are many deeper roles that these cells play. And research may find much more about them in the future.

There are six types of glial cells. Four of them are found in the CNS and two are found in the PNS. [\[link\]](#) outlines some common characteristics and functions.

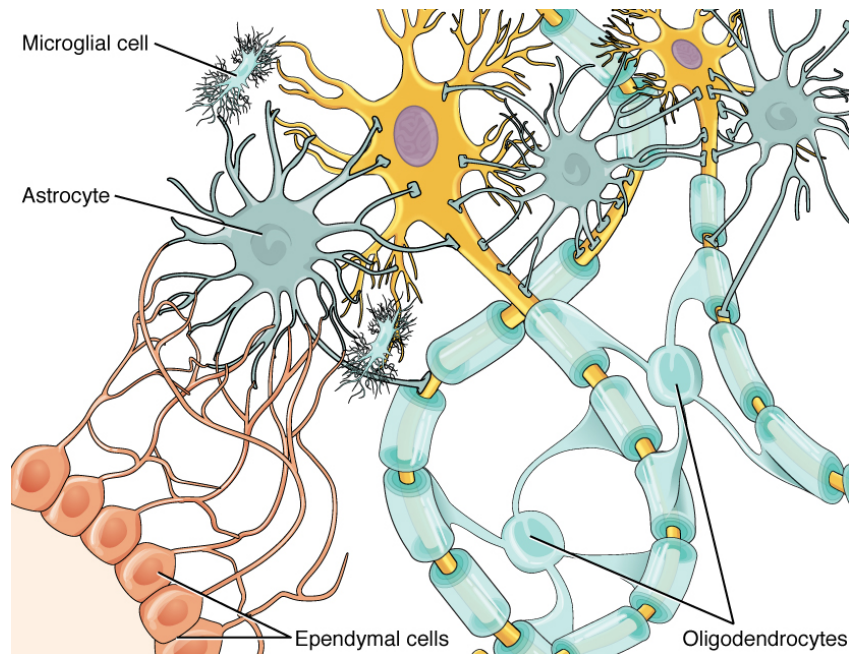
| Glial Cell Types by Location and Basic Function | | |
|---|----------------|--------------------------------------|
| CNS glia | PNS glia | Basic function |
| Astrocyte | Satellite cell | Support |
| Oligodendrocyte | Schwann cell | Insulation, myelination |
| Microglia | - | Immune surveillance and phagocytosis |
| Ependymal cell | - | Creating CSF |

Glial Cells of the CNS

One cell providing support to neurons of the CNS is the **astrocyte**, so named because it appears to be star-shaped under the microscope (astro- = “star”). Astrocytes have many processes extending from their main cell body (not axons or dendrites like neurons, just cell extensions). Those processes extend to interact with neurons, blood vessels, or the connective tissue covering the CNS that is called the pia mater ([\[link\]](#)). Generally, they are supporting cells for the neurons in the central nervous system. Some ways in which they support neurons in the central nervous system are by maintaining the concentration of chemicals in the extracellular space,

removing excess signaling molecules, reacting to tissue damage, and contributing to the **blood-brain barrier (BBB)**. The blood-brain barrier is a physiological barrier that keeps many substances that circulate in the rest of the body from getting into the central nervous system, restricting what can cross from circulating blood into the CNS. Nutrient molecules, such as glucose or amino acids, can pass through the BBB, but other molecules cannot. This actually causes problems with drug delivery to the CNS. Pharmaceutical companies are challenged to design drugs that can cross the BBB as well as have an effect on the nervous system.

Glial Cells of the CNS



The CNS has astrocytes, oligodendrocytes, microglia, and ependymal cells that support the neurons of the CNS in several ways.

Like a few other parts of the body, the brain has a privileged blood supply. Very little can pass through by diffusion. Most substances that cross the wall of a blood vessel into the CNS must do so through an active transport process. Because of this, only specific types of molecules can enter the CNS. Glucose—the primary energy source—is allowed, as are amino acids. Water and some other small particles, like gases and ions, can enter. But

most everything else cannot, including white blood cells, which are one of the body's main lines of defense. While this barrier protects the CNS from exposure to toxic or pathogenic substances, it also keeps out the cells that could protect the brain and spinal cord from disease and damage. The BBB also makes it harder for pharmaceuticals to be developed that can affect the nervous system. Aside from finding efficacious substances, the means of delivery is also crucial.

Also found in CNS tissue is the **oligodendrocyte**, sometimes called just "oligo," which is the glial cell type that insulates axons in the CNS. The name means "cell of a few branches" (oligo- = "few"; dendro- = "branches"; -cyte = "cell"). There are a few processes that extend from the cell body. Each one reaches out and surrounds an axon to insulate it in myelin. One oligodendrocyte will provide the myelin for multiple axon segments, either for the same axon or for separate axons. The function of myelin will be discussed below.

Microglia are, as the name implies, smaller than most of the other glial cells. Ongoing research into these cells, although not entirely conclusive, suggests that they may originate as white blood cells, called macrophages, that become part of the CNS during early development. While their origin is not conclusively determined, their function is related to what macrophages do in the rest of the body. When macrophages encounter diseased or damaged cells in the rest of the body, they ingest and digest those cells or the pathogens that cause disease. Microglia are the cells in the CNS that can do this in normal, healthy tissue, and they are therefore also referred to as CNS-resident macrophages.

The **ependymal cell** is a glial cell that filters blood to make **cerebrospinal fluid (CSF)**, the fluid that circulates through the CNS. Because of the privileged blood supply inherent in the BBB, the extracellular space in nervous tissue does not easily exchange components with the blood. Ependymal cells line each **ventricle**, one of four central cavities that are remnants of the hollow center of the neural tube formed during the embryonic development of the brain. The **choroid plexus** is a specialized structure in the ventricles where ependymal cells come in contact with blood vessels and filter and absorb components of the blood to produce

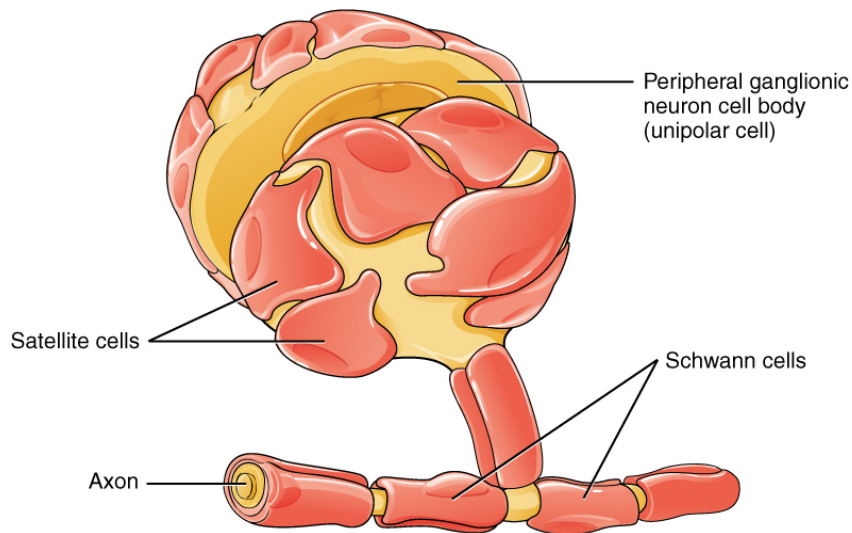
cerebrospinal fluid. Because of this, ependymal cells can be considered a component of the BBB, or a place where the BBB breaks down. These glial cells appear similar to epithelial cells, making a single layer of cells with little intracellular space and tight connections between adjacent cells. They also have cilia on their apical surface to help move the CSF through the ventricular space. The relationship of these glial cells to the structure of the CNS is seen in [\[link\]](#).

Glial Cells of the PNS

One of the two types of glial cells found in the PNS is the **satellite cell**. Satellite cells are found in sensory and autonomic ganglia, where they surround the cell bodies of neurons. This accounts for the name, based on their appearance under the microscope. They provide support, performing similar functions in the periphery as astrocytes do in the CNS—except, of course, for establishing the BBB.

The second type of glial cell is the **Schwann cell**, which insulate axons with myelin in the periphery. Schwann cells are different than oligodendrocytes, in that a Schwann cell wraps around a portion of only one axon segment and no others. Oligodendrocytes have processes that reach out to multiple axon segments, whereas the entire Schwann cell surrounds just one axon segment. The nucleus and cytoplasm of the Schwann cell are on the edge of the myelin sheath. The relationship of these two types of glial cells to ganglia and nerves in the PNS is seen in [\[link\]](#).

Glial Cells of the PNS



The PNS has satellite cells and Schwann cells.

Myelin

The insulation for axons in the nervous system is provided by glial cells, oligodendrocytes in the CNS, and Schwann cells in the PNS. Whereas the manner in which either cell is associated with the axon segment, or segments, that it insulates is different, the means of myelinating an axon segment is mostly the same in the two situations. Myelin is a lipid-rich sheath that surrounds the axon and by doing so creates a **myelin sheath** that facilitates the transmission of electrical signals along the axon. The lipids are essentially the phospholipids of the glial cell membrane. Myelin, however, is more than just the membrane of the glial cell. It also includes important proteins that are integral to that membrane. Some of the proteins help to hold the layers of the glial cell membrane closely together.

The appearance of the myelin sheath can be thought of as similar to the pastry wrapped around a hot dog for “pigs in a blanket” or a similar food. The glial cell is wrapped around the axon several times with little to no cytoplasm between the glial cell layers. For oligodendrocytes, the rest of the cell is separate from the myelin sheath as a cell process extends back

toward the cell body. A few other processes provide the same insulation for other axon segments in the area. For Schwann cells, the outermost layer of the cell membrane contains cytoplasm and the nucleus of the cell as a bulge on one side of the myelin sheath. During development, the glial cell is loosely or incompletely wrapped around the axon ([link](#)a). The edges of this loose enclosure extend toward each other, and one end tucks under the other. The inner edge wraps around the axon, creating several layers, and the other edge closes around the outside so that the axon is completely enclosed.

Note:

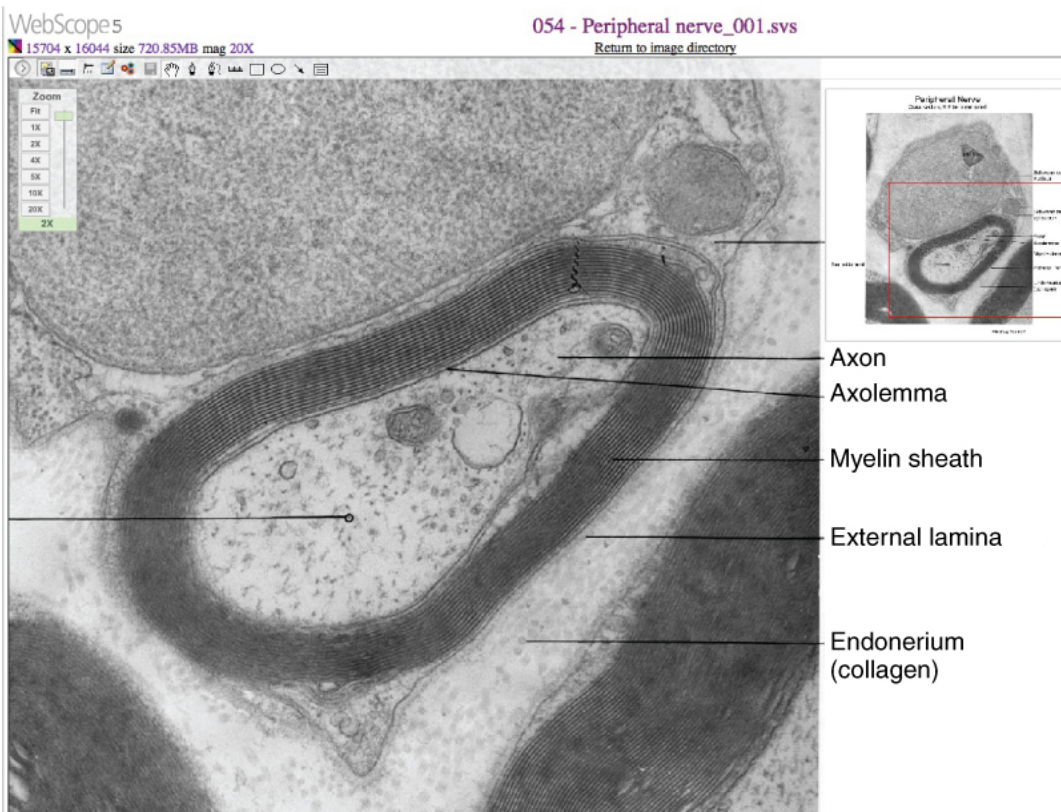
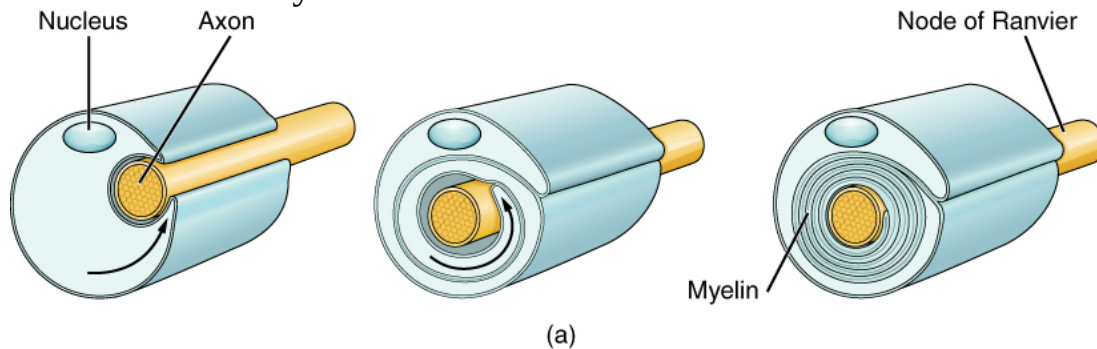


View the University of Michigan [WebScope](#) to see an electron micrograph of a cross-section of a myelinated nerve fiber. The axon contains microtubules and neurofilaments that are bounded by a plasma membrane known as the axolemma. Outside the plasma membrane of the axon is the myelin sheath, which is composed of the tightly wrapped plasma membrane of a Schwann cell. What aspects of the cells in this image react with the stain to make them a deep, dark, black color, such as the multiple layers that are the myelin sheath?

Myelin sheaths can extend for one or two millimeters, depending on the diameter of the axon. Axon diameters can be as small as 1 to 20 micrometers. Because a micrometer is 1/1000 of a millimeter, this means that the length of a myelin sheath can be 100–1000 times the diameter of the axon. [link](#), [link](#), and [link](#) show the myelin sheath surrounding an axon segment, but are not to scale. If the myelin sheath were drawn to scale,

the neuron would have to be immense—possibly covering an entire wall of the room in which you are sitting.

The Process of Myelination



Myelinating glia wrap several layers of cell membrane around the cell membrane of an axon segment. A single Schwann cell insulates a segment of a peripheral nerve, whereas in the CNS, an oligodendrocyte may provide insulation for a few separate axon segments. EM $\times 1,460,000$. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:

Disorders of the...

Nervous Tissue

Several diseases can result from the demyelination of axons. The causes of these diseases are not the same; some have genetic causes, some are caused by pathogens, and others are the result of autoimmune disorders. Though the causes are varied, the results are largely similar. The myelin insulation of axons is compromised, making electrical signaling slower.

Multiple sclerosis (MS) is one such disease. It is an example of an autoimmune disease. The antibodies produced by lymphocytes (a type of white blood cell) mark myelin as something that should not be in the body. This causes inflammation and the destruction of the myelin in the central nervous system. As the insulation around the axons is destroyed by the disease, scarring becomes obvious. This is where the name of the disease comes from; sclerosis means hardening of tissue, which is what a scar is. Multiple scars are found in the white matter of the brain and spinal cord. The symptoms of MS include both somatic and autonomic deficits. Control of the musculature is compromised, as is control of organs such as the bladder.

Guillain-Barré (pronounced gee-YAN bah-RAY) syndrome is an example of a demyelinating disease of the peripheral nervous system. It is also the result of an autoimmune reaction, but the inflammation is in peripheral nerves. Sensory symptoms or motor deficits are common, and autonomic failures can lead to changes in the heart rhythm or a drop in blood pressure, especially when standing, which causes dizziness.

Chapter Review

Nervous tissue contains two major cell types, neurons and glial cells. Neurons are the cells responsible for communication through electrical

signals. Glial cells are supporting cells, maintaining the environment around the neurons.

Neurons are polarized cells, based on the flow of electrical signals along their membrane. Signals are received at the dendrites, are passed along the cell body, and propagate along the axon towards the target, which may be another neuron, muscle tissue, or a gland. Many axons are insulated by a lipid-rich substance called myelin. Specific types of glial cells provide this insulation.

Several types of glial cells are found in the nervous system, and they can be categorized by the anatomical division in which they are found. In the CNS, astrocytes, oligodendrocytes, microglia, and ependymal cells are found. Astrocytes are important for maintaining the chemical environment around the neuron and are crucial for regulating the blood-brain barrier. Oligodendrocytes are the myelinating glia in the CNS. Microglia act as phagocytes and play a role in immune surveillance. Ependymal cells are responsible for filtering the blood to produce cerebrospinal fluid, which is a circulatory fluid that performs some of the functions of blood in the brain and spinal cord because of the BBB. In the PNS, satellite cells are supporting cells for the neurons, and Schwann cells insulate peripheral axons.

Interactive Link Questions

Exercise:

Problem:

Visit this [site](#) to learn about how nervous tissue is composed of neurons and glial cells. The neurons are dynamic cells with the ability to make a vast number of connections and to respond incredibly quickly to stimuli and to initiate movements based on those stimuli. They are the focus of intense research as failures in physiology can lead to devastating illnesses. Why are neurons only found in animals? Based on what this article says about neuron function, why wouldn't they be helpful for plants or microorganisms?

Solution:

Neurons enable thought, perception, and movement. Plants do not move, so they do not need this type of tissue. Microorganisms are too small to have a nervous system. Many are single-celled, and therefore have organelles for perception and movement.

Exercise:**Problem:**

View the University of Michigan [Webscope](#) to see an electron micrograph of a cross-section of a myelinated nerve fiber. The axon contains microtubules and neurofilaments, bounded by a plasma membrane known as the axolemma. Outside the plasma membrane of the axon is the myelin sheath, which is composed of the tightly wrapped plasma membrane of a Schwann cell. What aspects of the cells in this image react with the stain that makes them the deep, dark, black color, such as the multiple layers that are the myelin sheath?

Solution:

Lipid membranes, such as the cell membrane and organelle membranes.

Review Questions**Exercise:****Problem:**

What type of glial cell provides myelin for the axons in a tract?

- a. oligodendrocyte
 - b. astrocyte
 - c. Schwann cell
 - d. satellite cell
-

Solution:

A

Exercise:

Problem: Which part of a neuron contains the nucleus?

- a. dendrite
- b. soma
- c. axon
- d. synaptic end bulb

Solution:

B

Exercise:

Problem:

Which of the following substances is least able to cross the blood-brain barrier?

- a. water
- b. sodium ions
- c. glucose
- d. white blood cells

Solution:

D

Exercise:

Problem:

What type of glial cell is the resident macrophage behind the blood-brain barrier?

- a. microglia
- b. astrocyte
- c. Schwann cell
- d. satellite cell

Solution:

A

Exercise:**Problem:**

What two types of macromolecules are the main components of myelin?

- a. carbohydrates and lipids
- b. proteins and nucleic acids
- c. lipids and proteins
- d. carbohydrates and nucleic acids

Solution:

C

Critical Thinking Questions**Exercise:**

Problem:

Multiple sclerosis is a demyelinating disease affecting the central nervous system. What type of cell would be the most likely target of this disease? Why?

Solution:

The disease would target oligodendrocytes. In the CNS, oligodendrocytes provide the myelin for axons.

Exercise:**Problem:**

Which type of neuron, based on its shape, is best suited for relaying information directly from one neuron to another? Explain why.

Solution:

Bipolar cells, because they have one dendrite that receives input and one axon that provides output, would be a direct relay between two other cells.

Glossary**astrocyte**

glial cell type of the CNS that provides support for neurons and maintains the blood-brain barrier

axon hillock

tapering of the neuron cell body that gives rise to the axon

axon segment

single stretch of the axon insulated by myelin and bounded by nodes of Ranvier at either end (except for the first, which is after the initial segment, and the last, which is followed by the axon terminal)

axon terminal

end of the axon, where there are usually several branches extending toward the target cell

axoplasm

cytoplasm of an axon, which is different in composition than the cytoplasm of the neuronal cell body

bipolar

shape of a neuron with two processes extending from the neuron cell body—the axon and one dendrite

blood-brain barrier (BBB)

physiological barrier between the circulatory system and the central nervous system that establishes a privileged blood supply, restricting the flow of substances into the CNS

cerebrospinal fluid (CSF)

circulatory medium within the CNS that is produced by ependymal cells in the choroid plexus filtering the blood

choroid plexus

specialized structure containing ependymal cells that line blood capillaries and filter blood to produce CSF in the four ventricles of the brain

ependymal cell

glial cell type in the CNS responsible for producing cerebrospinal fluid

initial segment

first part of the axon as it emerges from the axon hillock, where the electrical signals known as action potentials are generated

microglia

glial cell type in the CNS that serves as the resident component of the immune system

multipolar

shape of a neuron that has multiple processes—the axon and two or more dendrites

myelin sheath

lipid-rich layer of insulation that surrounds an axon, formed by oligodendrocytes in the CNS and Schwann cells in the PNS; facilitates the transmission of electrical signals

node of Ranvier

gap between two myelinated regions of an axon, allowing for strengthening of the electrical signal as it propagates down the axon

oligodendrocyte

glial cell type in the CNS that provides the myelin insulation for axons in tracts

satellite cell

glial cell type in the PNS that provides support for neurons in the ganglia

Schwann cell

glial cell type in the PNS that provides the myelin insulation for axons in nerves

synapse

narrow junction across which a chemical signal passes from neuron to the next, initiating a new electrical signal in the target cell

synaptic end bulb

swelling at the end of an axon where neurotransmitter molecules are released onto a target cell across a synapse

unipolar

shape of a neuron which has only one process that includes both the axon and dendrite

ventricle

central cavity within the brain where CSF is produced and circulates

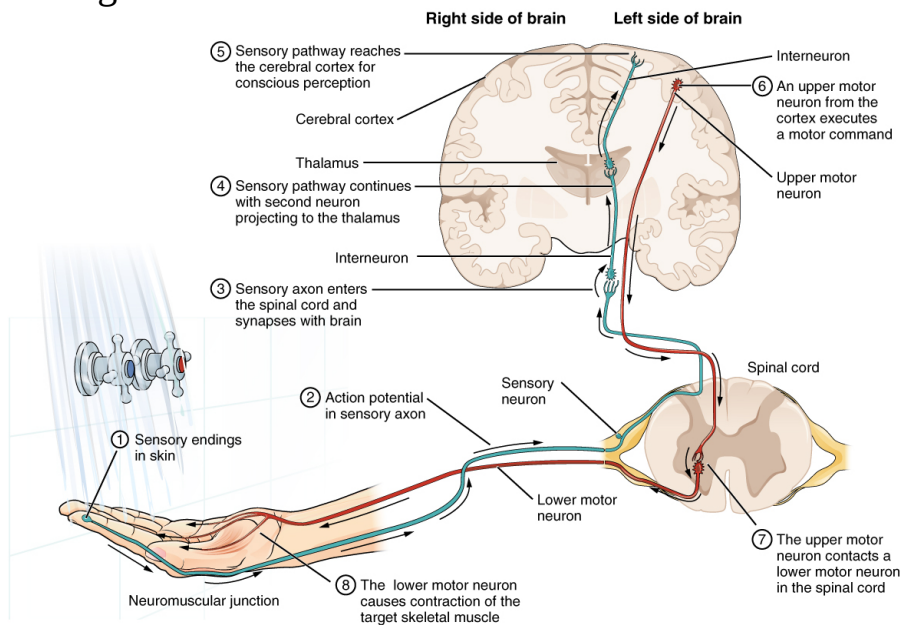
The Function of Nervous Tissue

By the end of this section, you will be able to:

- Distinguish the major functions of the nervous system: sensation, integration, and response
- List the sequence of events in a simple sensory receptor–motor response pathway

Having looked at the components of nervous tissue, and the basic anatomy of the nervous system, next comes an understanding of how nervous tissue is capable of communicating within the nervous system. Before getting to the nuts and bolts of how this works, an illustration of how the components come together will be helpful. An example is summarized in [\[link\]](#).

Testing the Water



- (1) The sensory neuron has endings in the skin that sense a stimulus such as water temperature. The strength of the signal that starts here is dependent on the strength of the stimulus. (2) The graded potential from the sensory endings, if strong enough, will initiate an action potential at the initial segment of the axon (which is immediately adjacent to the sensory endings in the skin). (3)

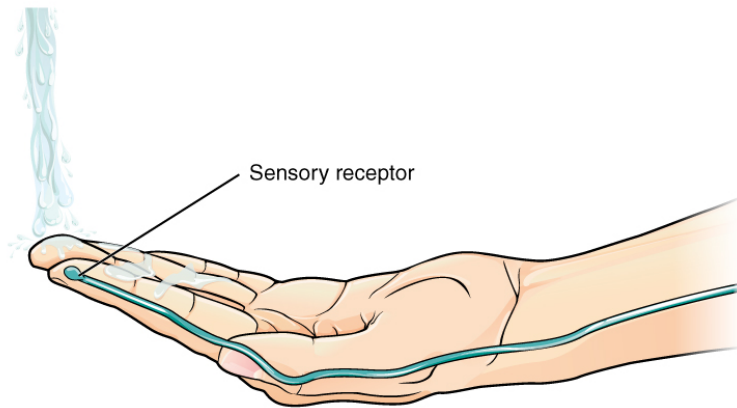
The axon of the peripheral sensory neuron enters the spinal cord and contacts another neuron in the gray matter. The contact is a synapse where another graded potential is caused by the release of a chemical signal from the axon terminals. (4) An action potential is initiated at the initial segment of this neuron and travels up the sensory pathway to a region of the brain called the thalamus. Another synapse passes the information along to the next neuron. (5) The sensory pathway ends when the signal reaches the cerebral cortex. (6) After integration with neurons in other parts of the cerebral cortex, a motor command is sent from the precentral gyrus of the frontal cortex. (7) The upper motor neuron sends an action potential down to the spinal cord. The target of the upper motor neuron is the dendrites of the lower motor neuron in the gray matter of the spinal cord. (8) The axon of the lower motor neuron emerges from the spinal cord in a nerve and connects to a muscle through a neuromuscular junction to cause contraction of the target muscle.

Imagine you are about to take a shower in the morning before going to school. You have turned on the faucet to start the water as you prepare to get in the shower. After a few minutes, you expect the water to be a temperature that will be comfortable to enter. So you put your hand out into the spray of water. What happens next depends on how your nervous system interacts with the stimulus of the water temperature and what you do in response to that stimulus.

Found in the skin of your fingers or toes is a type of sensory receptor that is sensitive to temperature, called a **thermoreceptor**. When you place your hand under the shower ([\[link\]](#)), the cell membrane of the thermoreceptors changes its electrical state (voltage). The amount of change is dependent on

the strength of the stimulus (how hot the water is). This is called a **graded potential**. If the stimulus is strong, the voltage of the cell membrane will change enough to generate an electrical signal that will travel down the axon. You have learned about this type of signaling before, with respect to the interaction of nerves and muscles at the neuromuscular junction. The voltage at which such a signal is generated is called the **threshold**, and the resulting electrical signal is called an **action potential**. In this example, the action potential travels—a process known as **propagation**—along the axon from the axon hillock to the axon terminals and into the synaptic end bulbs. When this signal reaches the end bulbs, it causes the release of a signaling molecule called a **neurotransmitter**.

The Sensory Input



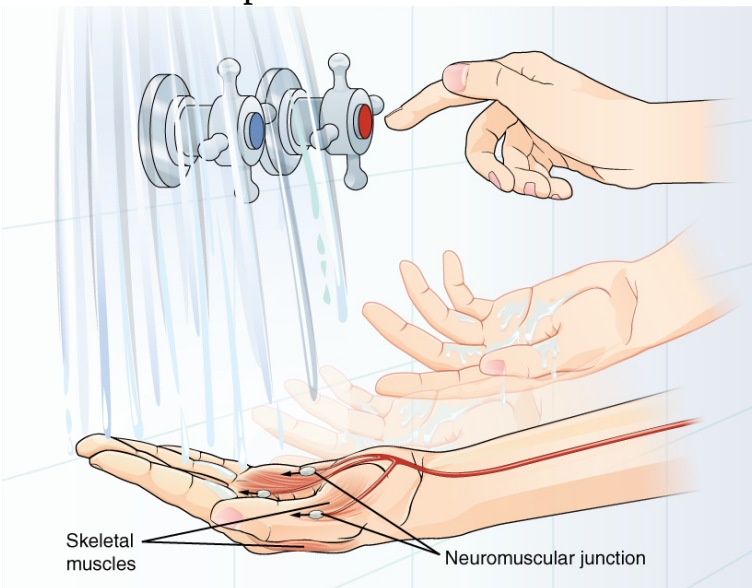
Receptors in the skin sense the temperature of the water.

The neurotransmitter diffuses across the short distance of the synapse and binds to a receptor protein of the target neuron. When the molecular signal binds to the receptor, the cell membrane of the target neuron changes its electrical state and a new graded potential begins. If that graded potential is strong enough to reach threshold, the second neuron generates an action potential at its axon hillock. The target of this neuron is another neuron in the **thalamus** of the brain, the part of the CNS that acts as a relay for sensory information. At another synapse, neurotransmitter is released and binds to its receptor. The thalamus then sends the sensory information to the

cerebral cortex, the outermost layer of gray matter in the brain, where conscious perception of that water temperature begins.

Within the cerebral cortex, information is processed among many neurons, integrating the stimulus of the water temperature with other sensory stimuli, with your emotional state (you just aren't ready to wake up; the bed is calling to you), memories (perhaps of the lab notes you have to study before a quiz). Finally, a plan is developed about what to do, whether that is to turn the temperature up, turn the whole shower off and go back to bed, or step into the shower. To do any of these things, the cerebral cortex has to send a command out to your body to move muscles ([link](#)).

The Motor Response



On the basis of the sensory input and the integration in the CNS, a motor response is formulated and executed.

A region of the cortex is specialized for sending signals down to the spinal cord for movement. The **upper motor neuron** is in this region, called the **precentral gyrus of the frontal cortex**, which has an axon that extends all the way down the spinal cord. At the level of the spinal cord at which this axon makes a synapse, a graded potential occurs in the cell membrane of a

lower motor neuron. This second motor neuron is responsible for causing muscle fibers to contract. In the manner described in the chapter on muscle tissue, an action potential travels along the motor neuron axon into the periphery. The axon terminates on muscle fibers at the neuromuscular junction. Acetylcholine is released at this specialized synapse, which causes the muscle action potential to begin, following a large potential known as an end plate potential. When the lower motor neuron excites the muscle fiber, it contracts. All of this occurs in a fraction of a second, but this story is the basis of how the nervous system functions.

Note:

Career Connections

Neurophysiologist

Understanding how the nervous system works could be a driving force in your career. Studying neurophysiology is a very rewarding path to follow. It means that there is a lot of work to do, but the rewards are worth the effort.

The career path of a research scientist can be straightforward: college, graduate school, postdoctoral research, academic research position at a university. A Bachelor's degree in science will get you started, and for neurophysiology that might be in biology, psychology, computer science, engineering, or neuroscience. But the real specialization comes in graduate school. There are many different programs out there to study the nervous system, not just neuroscience itself. Most graduate programs are doctoral, meaning that a Master's degree is not part of the work. These are usually considered five-year programs, with the first two years dedicated to course work and finding a research mentor, and the last three years dedicated to finding a research topic and pursuing that with a near single-mindedness. The research will usually result in a few publications in scientific journals, which will make up the bulk of a doctoral dissertation. After graduating with a Ph.D., researchers will go on to find specialized work called a postdoctoral fellowship within established labs. In this position, a researcher starts to establish their own research career with the hopes of finding an academic position at a research university.

Other options are available if you are interested in how the nervous system works. Especially for neurophysiology, a medical degree might be more suitable so you can learn about the clinical applications of neurophysiology and possibly work with human subjects. An academic career is not a necessity. Biotechnology firms are eager to find motivated scientists ready to tackle the tough questions about how the nervous system works so that therapeutic chemicals can be tested on some of the most challenging disorders such as Alzheimer's disease or Parkinson's disease, or spinal cord injury.

Others with a medical degree and a specialization in neuroscience go on to work directly with patients, diagnosing and treating mental disorders. You can do this as a psychiatrist, a neuropsychologist, a neuroscience nurse, or a neurodiagnostic technician, among other possible career paths.

Chapter Review

Sensation starts with the activation of a sensory ending, such as the thermoreceptor in the skin sensing the temperature of the water. The sensory endings in the skin initiate an electrical signal that travels along the sensory axon within a nerve into the spinal cord, where it synapses with a neuron in the gray matter of the spinal cord. The temperature information represented in that electrical signal is passed to the next neuron by a chemical signal that diffuses across the small gap of the synapse and initiates a new electrical signal in the target cell. That signal travels through the sensory pathway to the brain, passing through the thalamus, where conscious perception of the water temperature is made possible by the cerebral cortex. Following integration of that information with other cognitive processes and sensory information, the brain sends a command back down to the spinal cord to initiate a motor response by controlling a skeletal muscle. The motor pathway is composed of two cells, the upper motor neuron and the lower motor neuron. The upper motor neuron has its cell body in the cerebral cortex and synapses on a cell in the gray matter of the spinal cord. The lower motor neuron is that cell in the gray matter of the spinal cord and its axon extends into the periphery where it synapses with a skeletal muscle in a neuromuscular junction.

Review Questions

Exercise:

Problem:

If a thermoreceptor is sensitive to temperature sensations, what would a chemoreceptor be sensitive to?

- a. light
- b. sound
- c. molecules
- d. vibration

Solution:

C

Exercise:

Problem:

Which of these locations is where the greatest level of integration is taking place in the example of testing the temperature of the shower?

- a. skeletal muscle
- b. spinal cord
- c. thalamus
- d. cerebral cortex

Solution:

D

Exercise:

Problem:

How long does all the signaling through the sensory pathway, within the central nervous system, and through the motor command pathway take?

- a. 1 to 2 minutes
- b. 1 to 2 seconds
- c. fraction of a second
- d. varies with graded potential

Solution:

C

Exercise:

Problem:What is the target of an upper motor neuron?

- a. cerebral cortex
- b. lower motor neuron
- c. skeletal muscle
- d. thalamus

Solution:

B

Critical Thinking Questions**Exercise:**

Problem:

Sensory fibers, or pathways, are referred to as “afferent.” Motor fibers, or pathways, are referred to as “efferent.” What can you infer about the meaning of these two terms (afferent and efferent) in a structural or anatomical context?

Solution:

Afferent means “toward,” as in sensory information traveling from the periphery into the CNS. Efferent means “away from,” as in motor commands that travel from the brain down the spinal cord and out into the periphery.

Exercise:**Problem:**

If a person has a motor disorder and cannot move their arm voluntarily, but their muscles have tone, which motor neuron—upper or lower—is probably affected? Explain why.

Solution:

The upper motor neuron would be affected because it is carrying the command from the brain down.

Glossary**action potential**

change in voltage of a cell membrane in response to a stimulus that results in transmission of an electrical signal; unique to neurons and muscle fibers

cerebral cortex

outermost layer of gray matter in the brain, where conscious perception takes place

graded potential

change in the membrane potential that varies in size, depending on the size of the stimulus that elicits it

lower motor neuron

second neuron in the motor command pathway that is directly connected to the skeletal muscle

neurotransmitter

chemical signal that is released from the synaptic end bulb of a neuron to cause a change in the target cell

precentral gyrus of the frontal cortex

region of the cerebral cortex responsible for generating motor commands, where the upper motor neuron cell body is located

propagation

movement of an action potential along the length of an axon

thalamus

region of the central nervous system that acts as a relay for sensory pathways

thermoreceptor

type of sensory receptor capable of transducing temperature stimuli into neural action potentials

threshold

membrane voltage at which an action potential is initiated

upper motor neuron

first neuron in the motor command pathway with its cell body in the cerebral cortex that synapses on the lower motor neuron in the spinal cord

The Action Potential

By the end of this section, you will be able to:

- Describe the components of the membrane that establish the resting membrane potential
- Describe the changes that occur to the membrane that result in the action potential

The functions of the nervous system—sensation, integration, and response—depend on the functions of the neurons underlying these pathways. To understand how neurons are able to communicate, it is necessary to describe the role of an **excitable membrane** in generating these signals. The basis of this communication is the action potential, which demonstrates how changes in the membrane can constitute a signal. Looking at the way these signals work in more variable circumstances involves a look at graded potentials, which will be covered in the next section.

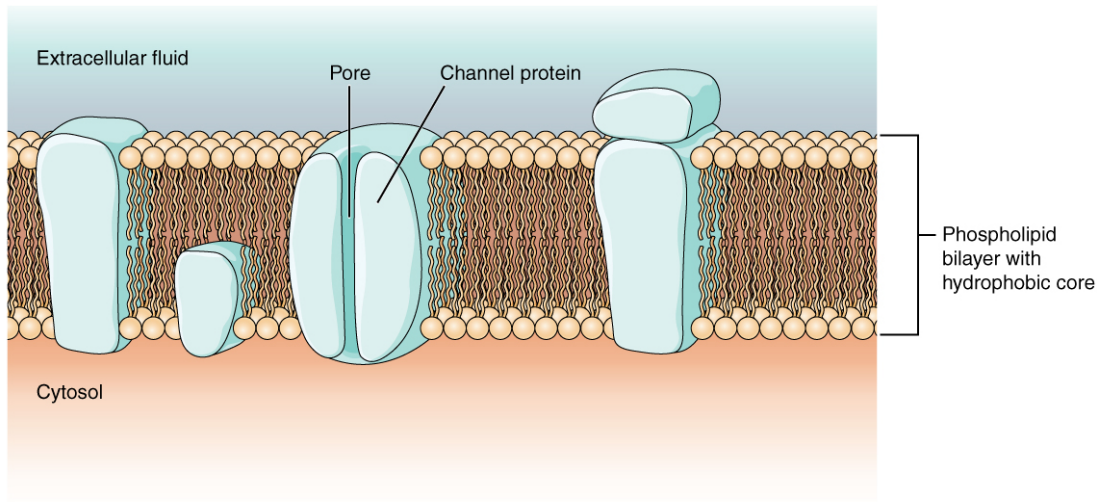
Electrically Active Cell Membranes

Most cells in the body make use of charged particles, ions, to build up a charge across the cell membrane. Previously, this was shown to be a part of how muscle cells work. For skeletal muscles to contract, based on excitation–contraction coupling, requires input from a neuron. Both of the cells make use of the cell membrane to regulate ion movement between the extracellular fluid and cytosol.

As you learned in the chapter on cells, the cell membrane is primarily responsible for regulating what can cross the membrane and what stays on only one side. The cell membrane is a phospholipid bilayer, so only substances that can pass directly through the hydrophobic core can diffuse through unaided. Charged particles, which are hydrophilic by definition, cannot pass through the cell membrane without assistance ([\[link\]](#)). Transmembrane proteins, specifically channel proteins, make this possible. Several passive transport channels, as well as active transport pumps, are necessary to generate a transmembrane potential and an action potential. Of special interest is the carrier protein referred to as the sodium/potassium pump that moves sodium ions (Na^+) out of a cell and potassium ions (K^+)

into a cell, thus regulating ion concentration on both sides of the cell membrane.

Cell Membrane and Transmembrane Proteins



The cell membrane is composed of a phospholipid bilayer and has many transmembrane proteins, including different types of channel proteins that serve as ion channels.

The sodium/potassium pump requires energy in the form of adenosine triphosphate (ATP), so it is also referred to as an ATPase. As was explained in the cell chapter, the concentration of Na^+ is higher outside the cell than inside, and the concentration of K^+ is higher inside the cell than outside. That means that this pump is moving the ions against the concentration gradients for sodium and potassium, which is why it requires energy. In fact, the pump basically maintains those concentration gradients.

Ion channels are pores that allow specific charged particles to cross the membrane in response to an existing concentration gradient. Proteins are capable of spanning the cell membrane, including its hydrophobic core, and can interact with the charge of ions because of the varied properties of amino acids found within specific domains or regions of the protein channel. Hydrophobic amino acids are found in the domains that are apposed to the hydrocarbon tails of the phospholipids. Hydrophilic amino acids are exposed to the fluid environments of the extracellular fluid and

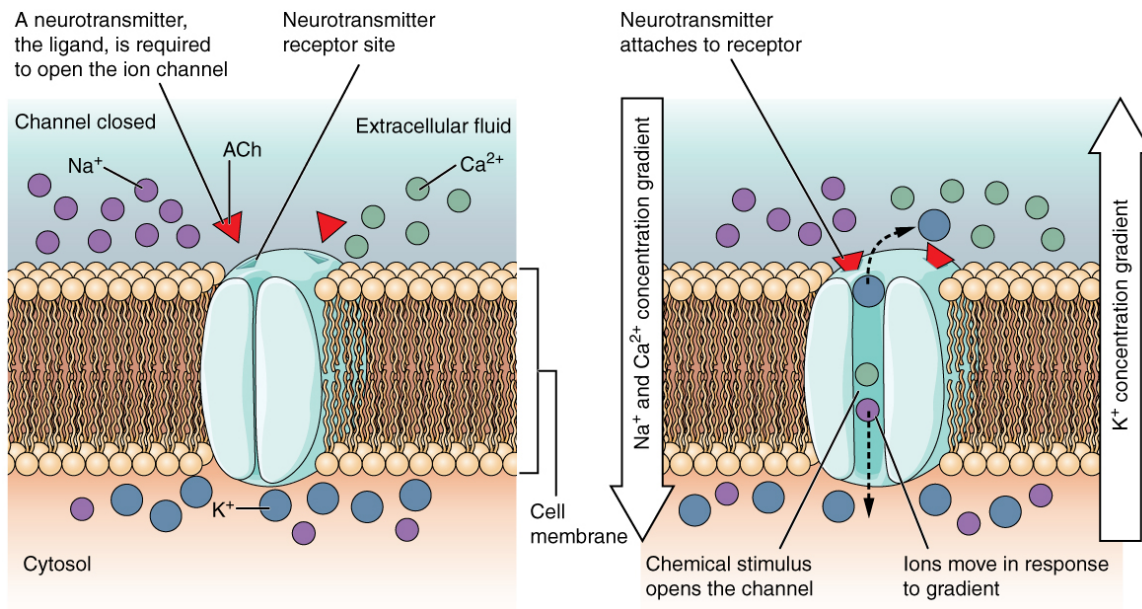
cytosol. Additionally, the ions will interact with the hydrophilic amino acids, which will be selective for the charge of the ion. Channels for cations (positive ions) will have negatively charged side chains in the pore. Channels for anions (negative ions) will have positively charged side chains in the pore. This is called **electrochemical exclusion**, meaning that the channel pore is charge-specific.

Ion channels can also be specified by the diameter of the pore. The distance between the amino acids will be specific for the diameter of the ion when it dissociates from the water molecules surrounding it. Because of the surrounding water molecules, larger pores are not ideal for smaller ions because the water molecules will interact, by hydrogen bonds, more readily than the amino acid side chains. This is called **size exclusion**. Some ion channels are selective for charge but not necessarily for size, and thus are called a **nonspecific channel**. These nonspecific channels allow cations—particularly Na^+ , K^+ , and Ca^{2+} —to cross the membrane, but exclude anions.

Ion channels do not always freely allow ions to diffuse across the membrane. Some are opened by certain events, meaning the channels are **gated**. So another way that channels can be categorized is on the basis of how they are gated. Although these classes of ion channels are found primarily in the cells of nervous or muscular tissue, they also can be found in the cells of epithelial and connective tissues.

A **ligand-gated channel** opens because a signaling molecule, a ligand, binds to the extracellular region of the channel. This type of channel is also known as an **ionotropic receptor** because when the ligand, known as a neurotransmitter in the nervous system, binds to the protein, ions cross the membrane changing its charge ([link](#)).

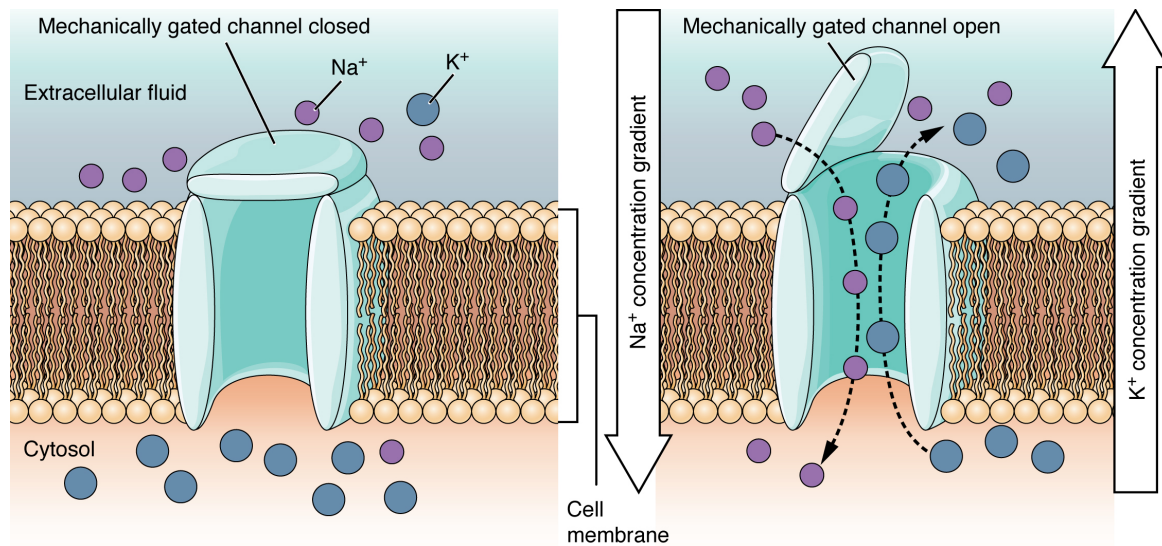
Ligand-Gated Channels



When the ligand, in this case the neurotransmitter acetylcholine, binds to a specific location on the extracellular surface of the channel protein, the pore opens to allow select ions through. The ions, in this case, are cations of sodium, calcium, and potassium.

A **mechanically gated channel** opens because of a physical distortion of the cell membrane. Many channels associated with the sense of touch (somatosensation) are mechanically gated. For example, as pressure is applied to the skin, these channels open and allow ions to enter the cell. Similar to this type of channel would be the channel that opens on the basis of temperature changes, as in testing the water in the shower ([link](#)).

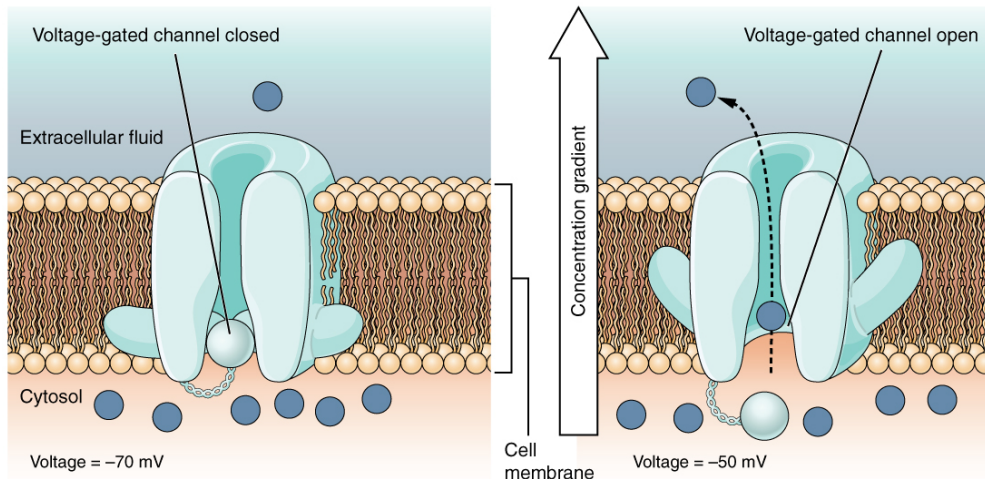
Mechanically Gated Channels



When a mechanical change occurs in the surrounding tissue, such as pressure or touch, the channel is physically opened. Thermoreceptors work on a similar principle. When the local tissue temperature changes, the protein reacts by physically opening the channel.

A **voltage-gated channel** is a channel that responds to changes in the electrical properties of the membrane in which it is embedded. Normally, the inner portion of the membrane is at a negative voltage. When that voltage becomes less negative, the channel begins to allow ions to cross the membrane ([link](#)).

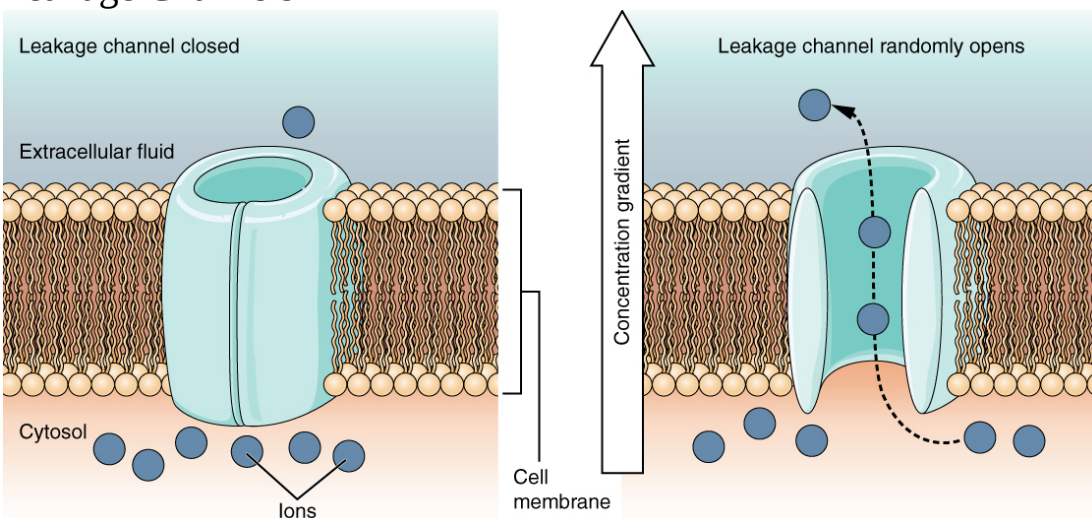
Voltage-Gated Channels



Voltage-gated channels open when the transmembrane voltage changes around them. Amino acids in the structure of the protein are sensitive to charge and cause the pore to open to the selected ion.

A **leakage channel** is randomly gated, meaning that it opens and closes at random, hence the reference to leaking. There is no actual event that opens the channel; instead, it has an intrinsic rate of switching between the open and closed states. Leakage channels contribute to the resting transmembrane voltage of the excitable membrane ([link](#)).

Leakage Channels

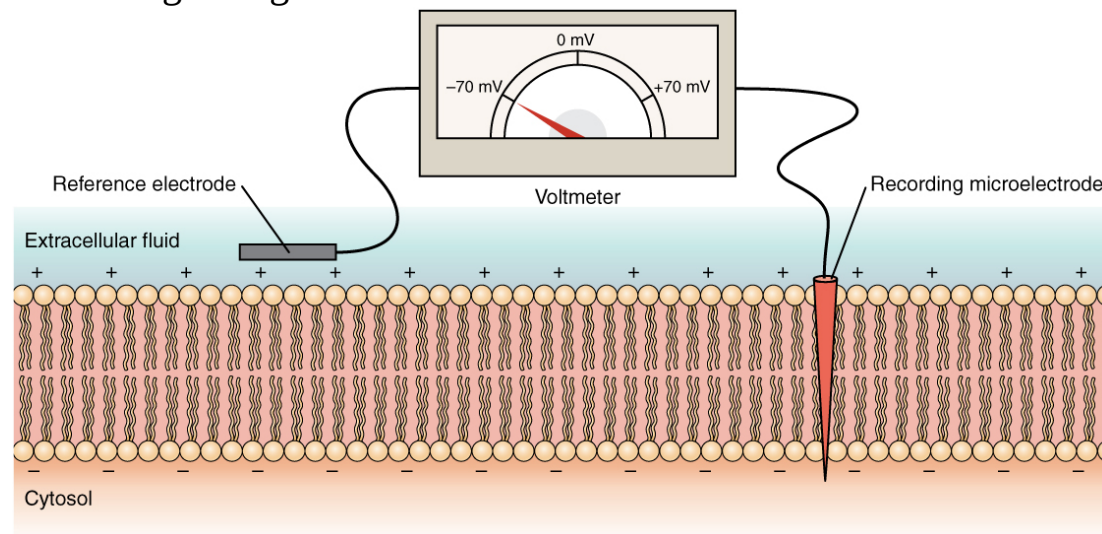


In certain situations, ions need to move across the membrane randomly. The particular electrical properties of certain cells are modified by the presence of this type of channel.

The Membrane Potential

The electrical state of the cell membrane can have several variations. These are all variations in the **membrane potential**. A potential is a distribution of charge across the cell membrane, measured in millivolts (mV). The standard is to compare the inside of the cell relative to the outside, so the membrane potential is a value representing the charge on the intracellular side of the membrane based on the outside being zero, relatively speaking ([link](#)).

Measuring Charge across a Membrane with a Voltmeter



A recording electrode is inserted into the cell and a reference electrode is outside the cell. By comparing the charge measured by these two electrodes, the transmembrane voltage is determined. It is conventional to express that value for the cytosol relative to the outside.

The concentration of ions in extracellular and intracellular fluids is largely balanced, with a net neutral charge. However, a slight difference in charge occurs right at the membrane surface, both internally and externally. It is the difference in this very limited region that has all the power in neurons (and muscle cells) to generate electrical signals, including action potentials.

Before these electrical signals can be described, the resting state of the membrane must be explained. When the cell is at rest, and the ion channels are closed (except for leakage channels which randomly open), ions are distributed across the membrane in a very predictable way. The concentration of Na^+ outside the cell is 10 times greater than the concentration inside. Also, the concentration of K^+ inside the cell is greater than outside. The cytosol contains a high concentration of anions, in the form of phosphate ions and negatively charged proteins. Large anions are a component of the inner cell membrane, including specialized phospholipids and proteins associated with the inner leaflet of the membrane (leaflet is a term used for one side of the lipid bilayer membrane). The negative charge is localized in the large anions.

With the ions distributed across the membrane at these concentrations, the difference in charge is measured at -70 mV, the value described as the **resting membrane potential**. The exact value measured for the resting membrane potential varies between cells, but -70 mV is most commonly used as this value. This voltage would actually be much lower except for the contributions of some important proteins in the membrane. Leakage channels allow Na^+ to slowly move into the cell or K^+ to slowly move out, and the Na^+/K^+ pump restores them. This may appear to be a waste of energy, but each has a role in maintaining the membrane potential.

The Action Potential

Resting membrane potential describes the steady state of the cell, which is a dynamic process that is balanced by ion leakage and ion pumping. Without any outside influence, it will not change. To get an electrical signal started, the membrane potential has to change.

This starts with a channel opening for Na^+ in the membrane. Because the concentration of Na^+ is higher outside the cell than inside the cell by a factor of 10, ions will rush into the cell that are driven largely by the concentration gradient. Because sodium is a positively charged ion, it will change the relative voltage immediately inside the cell relative to immediately outside. The resting potential is the state of the membrane at a voltage of -70 mV, so the sodium cation entering the cell will cause it to become less negative. This is known as **depolarization**, meaning the membrane potential moves toward zero.

The concentration gradient for Na^+ is so strong that it will continue to enter the cell even after the membrane potential has become zero, so that the voltage immediately around the pore begins to become positive. The electrical gradient also plays a role, as negative proteins below the membrane attract the sodium ion. The membrane potential will reach +30 mV by the time sodium has entered the cell.

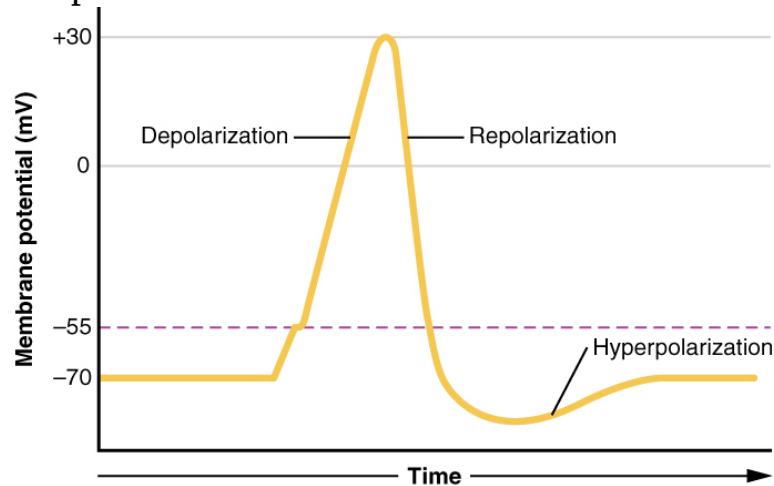
As the membrane potential reaches +30 mV, other voltage-gated channels are opening in the membrane. These channels are specific for the potassium ion. A concentration gradient acts on K^+ , as well. As K^+ starts to leave the cell, taking a positive charge with it, the membrane potential begins to move back toward its resting voltage. This is called **repolarization**, meaning that the membrane voltage moves back toward the -70 mV value of the resting membrane potential.

Repolarization returns the membrane potential to the -70 mV value that indicates the resting potential, but it actually overshoots that value. Potassium ions reach equilibrium when the membrane voltage is below -70 mV, so a period of hyperpolarization occurs while the K^+ channels are open. Those K^+ channels are slightly delayed in closing, accounting for this short overshoot.

What has been described here is the action potential, which is presented as a graph of voltage over time in [\[link\]](#). It is the electrical signal that nervous tissue generates for communication. The change in the membrane voltage from -70 mV at rest to +30 mV at the end of depolarization is a 100-mV change. That can also be written as a 0.1-V change. To put that value in perspective, think about a battery. An AA battery that you might find in a

television remote has a voltage of 1.5 V, or a 9-V battery (the rectangular battery with two posts on one end) is, obviously, 9 V. The change seen in the action potential is one or two orders of magnitude less than the charge in these batteries. In fact, the membrane potential can be described as a battery. A charge is stored across the membrane that can be released under the correct conditions. A battery in your remote has stored a charge that is “released” when you push a button.

Graph of Action Potential



Plotting voltage measured across the cell membrane against time, the action potential begins with depolarization, followed by repolarization, which goes past the resting potential into hyperpolarization, and finally the membrane returns to rest.

Note:



What happens across the membrane of an electrically active cell is a dynamic process that is hard to visualize with static images or through text descriptions. View this [animation](#) to learn more about this process. What is the difference between the driving force for Na^+ and K^+ ? And what is similar about the movement of these two ions?

The question is, now, what initiates the action potential? The description above conveniently glosses over that point. But it is vital to understanding what is happening. The membrane potential will stay at the resting voltage until something changes. The description above just says that a Na^+ channel opens. Now, to say “a channel opens” does not mean that one individual transmembrane protein changes. Instead, it means that one kind of channel opens. There are a few different types of channels that allow Na^+ to cross the membrane. A ligand-gated Na^+ channel will open when a neurotransmitter binds to it and a mechanically gated Na^+ channel will open when a physical stimulus affects a sensory receptor (like pressure applied to the skin compresses a touch receptor). Whether it is a neurotransmitter binding to its receptor protein or a sensory stimulus activating a sensory receptor cell, some stimulus gets the process started. Sodium starts to enter the cell and the membrane becomes less negative.

A third type of channel that is an important part of depolarization in the action potential is the voltage-gated Na^+ channel. The channels that start depolarizing the membrane because of a stimulus help the cell to depolarize from -70 mV to -55 mV . Once the membrane reaches that voltage, the voltage-gated Na^+ channels open. This is what is known as the threshold. Any depolarization that does not change the membrane potential to -55 mV or higher will not reach threshold and thus will not result in an action potential. Also, any stimulus that depolarizes the membrane to -55 mV or

beyond will cause a large number of channels to open and an action potential will be initiated.

Because of the threshold, the action potential can be likened to a digital event—it either happens or it does not. If the threshold is not reached, then no action potential occurs. If depolarization reaches -55 mV , then the action potential continues and runs all the way to $+30\text{ mV}$, at which K^+ causes repolarization, including the hyperpolarizing overshoot. Also, those changes are the same for every action potential, which means that once the threshold is reached, the exact same thing happens. A stronger stimulus, which might depolarize the membrane well past threshold, will not make a “bigger” action potential. Action potentials are “all or none.” Either the membrane reaches the threshold and everything occurs as described above, or the membrane does not reach the threshold and nothing else happens. All action potentials peak at the same voltage ($+30\text{ mV}$), so one action potential is not bigger than another. Stronger stimuli will initiate multiple action potentials more quickly, but the individual signals are not bigger. Thus, for example, you will not feel a greater sensation of pain, or have a stronger muscle contraction, because of the size of the action potential because they are not different sizes.

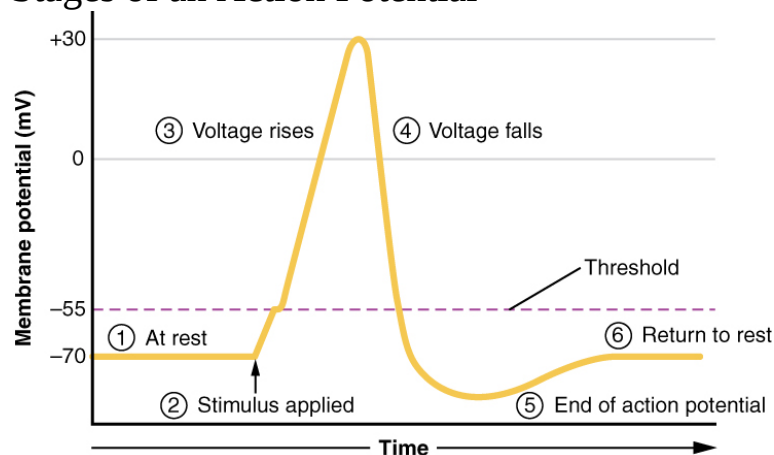
As we have seen, the depolarization and repolarization of an action potential are dependent on two types of channels (the voltage-gated Na^+ channel and the voltage-gated K^+ channel). The voltage-gated Na^+ channel actually has two gates. One is the **activation gate**, which opens when the membrane potential crosses -55 mV . The other gate is the **inactivation gate**, which closes after a specific period of time—on the order of a fraction of a millisecond. When a cell is at rest, the activation gate is closed and the inactivation gate is open. However, when the threshold is reached, the activation gate opens, allowing Na^+ to rush into the cell. Timed with the peak of depolarization, the inactivation gate closes. During repolarization, no more sodium can enter the cell. When the membrane potential passes -55 mV again, the activation gate closes. After that, the inactivation gate re-opens, making the channel ready to start the whole process over again.

The voltage-gated K^+ channel has only one gate, which is sensitive to a membrane voltage of -50 mV . However, it does not open as quickly as the

voltage-gated Na^+ channel does. It might take a fraction of a millisecond for the channel to open once that voltage has been reached. The timing of this coincides exactly with when the Na^+ flow peaks, so voltage-gated K^+ channels open just as the voltage-gated Na^+ channels are being inactivated. As the membrane potential repolarizes and the voltage passes -50 mV again, the channel closes—again, with a little delay. Potassium continues to leave the cell for a short while and the membrane potential becomes more negative, resulting in the hyperpolarizing overshoot. Then the channel closes again and the membrane can return to the resting potential because of the ongoing activity of the non-gated channels and the Na^+/K^+ pump.

All of this takes place within approximately 2 milliseconds ([\[link\]](#)). While an action potential is in progress, another one cannot be initiated. That effect is referred to as the **refractory period**. There are two phases of the refractory period: the **absolute refractory period** and the **relative refractory period**. During the absolute phase, another action potential will not start. This is because of the inactivation gate of the voltage-gated Na^+ channel. Once that channel is back to its resting conformation (less than -55 mV), a new action potential could be started, but only by a stronger stimulus than the one that initiated the current action potential. This is because of the flow of K^+ out of the cell. Because that ion is rushing out, any Na^+ that tries to enter will not depolarize the cell, but will only keep the cell from hyperpolarizing.

Stages of an Action Potential



Plotting voltage measured across the cell membrane against time, the events of the

action potential can be related to specific changes in the membrane voltage. (1) At rest, the membrane voltage is -70 mV. (2) The membrane begins to depolarize when an external stimulus is applied. (3) The membrane voltage begins a rapid rise toward +30 mV. (4) The membrane voltage starts to return to a negative value. (5) Repolarization continues past the resting membrane voltage, resulting in hyperpolarization. (6) The membrane voltage returns to the resting value shortly after hyperpolarization.

Propagation of the Action Potential

The action potential is initiated at the beginning of the axon, at what is called the initial segment. There is a high density of voltage-gated Na^+ channels so that rapid depolarization can take place here. Going down the length of the axon, the action potential is propagated because more voltage-gated Na^+ channels are opened as the depolarization spreads. This spreading occurs because Na^+ enters through the channel and moves along the inside of the cell membrane. As the Na^+ moves, or flows, a short distance along the cell membrane, its positive charge depolarizes a little more of the cell membrane. As that depolarization spreads, new voltage-gated Na^+ channels open and more ions rush into the cell, spreading the depolarization a little farther.

Because voltage-gated Na^+ channels are inactivated at the peak of the depolarization, they cannot be opened again for a brief time—the absolute refractory period. Because of this, depolarization spreading back toward previously opened channels has no effect. The action potential must propagate toward the axon terminals; as a result, the polarity of the neuron is maintained, as mentioned above.

Propagation, as described above, applies to unmyelinated axons. When myelination is present, the action potential propagates differently. Sodium ions that enter the cell at the initial segment start to spread along the length of the axon segment, but there are no voltage-gated Na^+ channels until the first node of Ranvier. Because there is not constant opening of these channels along the axon segment, the depolarization spreads at an optimal speed. The distance between nodes is the optimal distance to keep the membrane still depolarized above threshold at the next node. As Na^+ spreads along the inside of the membrane of the axon segment, the charge starts to dissipate. If the node were any farther down the axon, that depolarization would have fallen off too much for voltage-gated Na^+ channels to be activated at the next node of Ranvier. If the nodes were any closer together, the speed of propagation would be slower.

Propagation along an unmyelinated axon is referred to as **continuous conduction**; along the length of a myelinated axon, it is **saltatory conduction**. Continuous conduction is slow because there are always voltage-gated Na^+ channels opening, and more and more Na^+ is rushing into the cell. Saltatory conduction is faster because the action potential basically jumps from one node to the next (saltare = “to leap”), and the new influx of Na^+ renews the depolarized membrane. Along with the myelination of the axon, the diameter of the axon can influence the speed of conduction. Much as water runs faster in a wide river than in a narrow creek, Na^+ -based depolarization spreads faster down a wide axon than down a narrow one. This concept is known as **resistance** and is generally true for electrical wires or plumbing, just as it is true for axons, although the specific conditions are different at the scales of electrons or ions versus water in a river.

Note:**Homeostatic Imbalances****Potassium Concentration**

Glial cells, especially astrocytes, are responsible for maintaining the chemical environment of the CNS tissue. The concentrations of ions in the extracellular fluid are the basis for how the membrane potential is

established and changes in electrochemical signaling. If the balance of ions is upset, drastic outcomes are possible.

Normally the concentration of K^+ is higher inside the neuron than outside. After the repolarizing phase of the action potential, K^+ leakage channels and the Na^+/K^+ pump ensure that the ions return to their original locations. Following a stroke or other ischemic event, extracellular K^+ levels are elevated. The astrocytes in the area are equipped to clear excess K^+ to aid the pump. But when the level is far out of balance, the effects can be irreversible.

Astrocytes can become reactive in cases such as these, which impairs their ability to maintain the local chemical environment. The glial cells enlarge and their processes swell. They lose their K^+ buffering ability and the function of the pump is affected, or even reversed. One of the early signs of cell disease is this "leaking" of sodium ions into the body cells. This sodium/potassium imbalance negatively affects the internal chemistry of cells, preventing them from functioning normally.

Note:



Visit this [site](#) to see a virtual neurophysiology lab, and to observe electrophysiological processes in the nervous system, where scientists directly measure the electrical signals produced by neurons. Often, the action potentials occur so rapidly that watching a screen to see them occur is not helpful. A speaker is powered by the signals recorded from a neuron and it “pops” each time the neuron fires an action potential. These action potentials are firing so fast that it sounds like static on the radio. Electrophysiologists can recognize the patterns within that static to understand what is happening. Why is the leech model used for measuring the electrical activity of neurons instead of using humans?

Chapter Review

The nervous system is characterized by electrical signals that are sent from one area to another. Whether those areas are close or very far apart, the signal must travel along an axon. The basis of the electrical signal is the controlled distribution of ions across the membrane. Transmembrane ion channels regulate when ions can move in or out of the cell, so that a precise signal is generated. This signal is the action potential which has a very characteristic shape based on voltage changes across the membrane in a given time period.

The membrane is normally at rest with established Na^+ and K^+ concentrations on either side. A stimulus will start the depolarization of the membrane, and voltage-gated channels will result in further depolarization followed by repolarization of the membrane. A slight overshoot of hyperpolarization marks the end of the action potential. While an action potential is in progress, another cannot be generated under the same conditions. While the voltage-gated Na^+ channel is inactivated, absolutely no action potentials can be generated. Once that channel has returned to its resting state, a new action potential is possible, but it must be started by a relatively stronger stimulus to overcome the K^+ leaving the cell.

The action potential travels down the axon as voltage-gated ion channels are opened by the spreading depolarization. In unmyelinated axons, this happens in a continuous fashion because there are voltage-gated channels throughout the membrane. In myelinated axons, propagation is described as saltatory because voltage-gated channels are only found at the nodes of Ranvier and the electrical events seem to “jump” from one node to the next. Saltatory conduction is faster than continuous conduction, meaning that myelinated axons propagate their signals faster. The diameter of the axon also makes a difference as ions diffusing within the cell have less resistance in a wider space.

Interactive Link Questions

Exercise:

Problem:

What happens across the membrane of an electrically active cell is a dynamic process that is hard to visualize with static images or through text descriptions. View this [animation](#) to really understand the process. What is the difference between the driving force for Na^+ and K^+ ? And what is similar about the movement of these two ions?

Solution:

Sodium is moving into the cell because of the immense concentration gradient, whereas potassium is moving out because of the depolarization that sodium causes. However, they both move down their respective gradients, toward equilibrium.

Exercise:**Problem:**

Visit this [site](#) to see a virtual neurophysiology lab, and to observe electrophysiological processes in the nervous system, where scientists directly measure the electrical signals produced by neurons. Often, the action potentials occur so rapidly that watching a screen to see them occur is not helpful. A speaker is powered by the signals recorded from a neuron and it “pops” each time the neuron fires an action potential. These action potentials are firing so fast that it sounds like static on the radio. Electrophysiologists can recognize the patterns within that static to understand what is happening. Why is the leech model used for measuring the electrical activity of neurons instead of using humans?

Solution:

The properties of electrophysiology are common to all animals, so using the leech is an easier, more humane approach to studying the properties of these cells. There are differences between the nervous systems of invertebrates (such as a leech) and vertebrates, but not for the sake of what these experiments study.

Review Questions

Exercise:

Problem:

What ion enters a neuron causing depolarization of the cell membrane?

- a. sodium
- b. chloride
- c. potassium
- d. phosphate

Solution:

A

Exercise:

Problem: Voltage-gated Na^+ channels open upon reaching what state?

- a. resting potential
- b. threshold
- c. repolarization
- d. overshoot

Solution:

B

Exercise:

Problem: What does a ligand-gated channel require in order to open?

- a. increase in concentration of Na^+ ions
- b. binding of a neurotransmitter
- c. increase in concentration of K^+ ions

d. depolarization of the membrane

Solution:

B

Exercise:

Problem: What does a mechanically gated channel respond to?

- a. physical stimulus
 - b. chemical stimulus
 - c. increase in resistance
 - d. decrease in resistance
-

Solution:

A

Exercise:

Problem:

Which of the following voltages would most likely be measured during the relative refractory period?

- a. +30 mV
 - b. 0 mV
 - c. -45 mV
 - d. -80 mv
-

Solution:

D

Exercise:

Problem:

Which of the following is probably going to propagate an action potential fastest?

- a. a thin, unmyelinated axon
- b. a thin, myelinated axon
- c. a thick, unmyelinated axon
- d. a thick, myelinated axon

Solution:

D

Critical Thinking Questions**Exercise:****Problem:**

What does it mean for an action potential to be an “all or none” event?

Solution:

The cell membrane must reach threshold before voltage-gated Na^+ channels open. If threshold is not reached, those channels do not open, and the depolarizing phase of the action potential does not occur, the cell membrane will just go back to its resting state.

Exercise:**Problem:**

The conscious perception of pain is often delayed because of the time it takes for the sensations to reach the cerebral cortex. Why would this be the case based on propagation of the axon potential?

Solution:

Axons of pain sensing sensory neurons are thin and unmyelinated so that it takes longer for that sensation to reach the brain than other sensations.

Glossary

absolute refractory period

time during an action period when another action potential cannot be generated because the voltage-gated Na^+ channel is inactivated

activation gate

part of the voltage-gated Na^+ channel that opens when the membrane voltage reaches threshold

continuous conduction

slow propagation of an action potential along an unmyelinated axon owing to voltage-gated Na^+ channels located along the entire length of the cell membrane

depolarization

change in a cell membrane potential from rest toward zero

electrochemical exclusion

principle of selectively allowing ions through a channel on the basis of their charge

excitable membrane

cell membrane that regulates the movement of ions so that an electrical signal can be generated

gated

property of a channel that determines how it opens under specific conditions, such as voltage change or physical deformation

inactivation gate

part of a voltage-gated Na^+ channel that closes when the membrane potential reaches +30 mV

ionotropic receptor

neurotransmitter receptor that acts as an ion channel gate, and opens by the binding of the neurotransmitter

leakage channel

ion channel that opens randomly and is not gated to a specific event, also known as a non-gated channel

ligand-gated channels

another name for an ionotropic receptor for which a neurotransmitter is the ligand

mechanically gated channel

ion channel that opens when a physical event directly affects the structure of the protein

membrane potential

distribution of charge across the cell membrane, based on the charges of ions

nonspecific channel

channel that is not specific to one ion over another, such as a nonspecific cation channel that allows any positively charged ion across the membrane

refractory period

time after the initiation of an action potential when another action potential cannot be generated

relative refractory period

time during the refractory period when a new action potential can only be initiated by a stronger stimulus than the current action potential because voltage-gated K^+ channels are not closed

repolarization

return of the membrane potential to its normally negative voltage at the end of the action potential

resistance

property of an axon that relates to the ability of particles to diffuse through the cytoplasm; this is inversely proportional to the fiber diameter

resting membrane potential

the difference in voltage measured across a cell membrane under steady-state conditions, typically -70 mV

saltatory conduction

quick propagation of the action potential along a myelinated axon owing to voltage-gated Na^+ channels being present only at the nodes of Ranvier

size exclusion

principle of selectively allowing ions through a channel on the basis of their relative size

voltage-gated channel

ion channel that opens because of a change in the charge distributed across the membrane where it is located

Communication Between Neurons

By the end of this section, you will be able to:

- Explain the differences between the types of graded potentials
- Categorize the major neurotransmitters by chemical type and effect

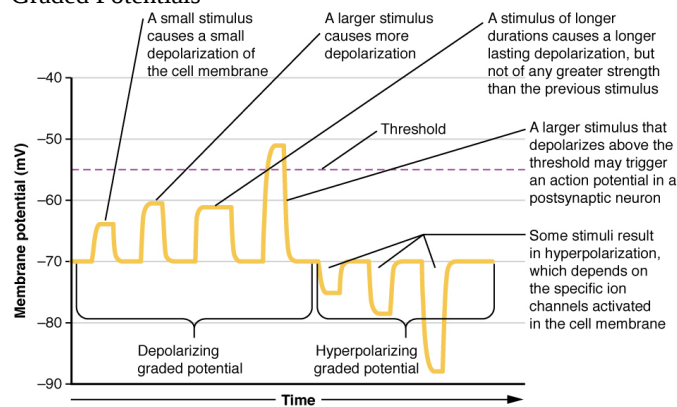
The electrical changes taking place within a neuron, as described in the previous section, are similar to a light switch being turned on. A stimulus starts the depolarization, but the action potential runs on its own once a threshold has been reached. The question is now, “What flips the light switch on?” Temporary changes to the cell membrane voltage can result from neurons receiving information from the environment, or from the action of one neuron on another. These special types of potentials influence a neuron and determine whether an action potential will occur or not. Many of these transient signals originate at the synapse.

Graded Potentials

Local changes in the membrane potential are called graded potentials and are usually associated with the dendrites of a neuron. The amount of change in the membrane potential is determined by the size of the stimulus that causes it. In the example of testing the temperature of the shower, slightly warm water would only initiate a small change in a thermoreceptor, whereas hot water would cause a large amount of change in the membrane potential.

Graded potentials can be of two sorts, either they are depolarizing or hyperpolarizing ([link](#)). For a membrane at the resting potential, a graded potential represents a change in that voltage either above -70 mV or below -70 mV. Depolarizing graded potentials are often the result of Na^+ or Ca^{2+} entering the cell. Both of these ions have higher concentrations outside the cell than inside; because they have a positive charge, they will move into the cell causing it to become less negative relative to the outside. Hyperpolarizing graded potentials can be caused by K^+ leaving the cell or Cl^- entering the cell. If a positive charge moves out of a cell, the cell becomes more negative; if a negative charge enters the cell, the same thing happens.

Graded Potentials



Graded potentials are temporary changes in the membrane voltage, the characteristics of which depend on the size of the stimulus. Some types of stimuli cause depolarization of the membrane, whereas others cause hyperpolarization. It depends on the specific ion channels that are activated in the cell membrane.

Types of Graded Potentials

For the unipolar cells of sensory neurons—both those with free nerve endings and those within encapsulations—graded potentials develop in the dendrites that influence the generation of an action potential in the axon of the same cell. This is called a **generator potential**. For other sensory receptor cells, such as taste cells or photoreceptors of the retina, graded potentials in their membranes result in the release of neurotransmitters at synapses with sensory neurons. This is called a **receptor potential**.

A **postsynaptic potential (PSP)** is the graded potential in the dendrites of a neuron that is receiving synapses from other cells. Postsynaptic potentials can be depolarizing or hyperpolarizing. Depolarization in a postsynaptic potential is called an **excitatory postsynaptic potential (EPSP)** because it causes the membrane potential to move toward threshold. Hyperpolarization in a postsynaptic potential is an **inhibitory postsynaptic potential (IPSP)** because it causes the membrane potential to move away from threshold.

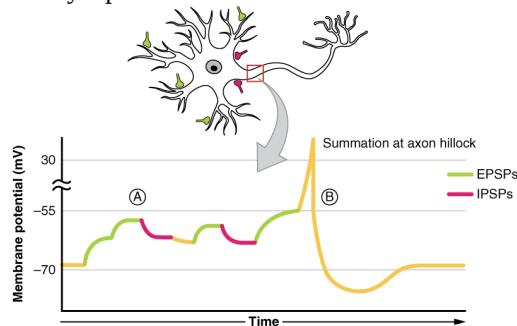
Summation

All types of graded potentials will result in small changes of either depolarization or hyperpolarization in the voltage of a membrane. These changes can lead to the neuron reaching threshold if the changes add together, or **summate**. The combined effects of different types of graded potentials are illustrated in [\[link\]](#). If the total change in voltage in the membrane is a positive 15 mV, meaning that the membrane depolarizes from -70 mV to -55 mV, then the graded potentials will result in the membrane reaching threshold.

For receptor potentials, threshold is not a factor because the change in membrane potential for receptor cells directly causes neurotransmitter release. However, generator potentials can initiate action potentials in the sensory neuron axon, and postsynaptic potentials can initiate an action potential in the axon of other neurons. Graded potentials summate at a specific location at the beginning of the axon to initiate the action potential, namely the initial segment. For sensory neurons, which do not have a cell body between the dendrites and the axon, the initial segment is directly adjacent to the dendritic endings. For all other neurons, the axon hillock is essentially the initial segment of the axon, and it is where summation takes place. These locations have a high density of voltage-gated Na^+ channels that initiate the depolarizing phase of the action potential.

Summation can be spatial or temporal, meaning it can be the result of multiple graded potentials at different locations on the neuron, or all at the same place but separated in time. **Spatial summation** is related to associating the activity of multiple inputs to a neuron with each other. **Temporal summation** is the relationship of multiple action potentials from a single cell resulting in a significant change in the membrane potential. Spatial and temporal summation can act together, as well.

Postsynaptic Potential Summation



The result of summation of postsynaptic potentials is the overall change in the membrane potential. At point A, several different excitatory postsynaptic potentials add up to a large depolarization. At point B, a mix of excitatory and inhibitory postsynaptic

potentials result in a different end result for the membrane potential.

Note:



Watch this [video](#) to learn about summation. The process of converting electrical signals to chemical signals and back requires subtle changes that can result in transient increases or decreases in membrane voltage. To cause a lasting change in the target cell, multiple signals are usually added together, or summated. Does spatial summation have to happen all at once, or can the separate signals arrive on the postsynaptic neuron at slightly different times? Explain your answer.

Synapses

There are two types of connections between electrically active cells, chemical synapses and electrical synapses. In a **chemical synapse**, a chemical signal—namely, a neurotransmitter—is released from one cell and it affects the other cell. In an **electrical synapse**, there is a direct connection between the two cells so that ions can pass directly from one cell to the next. If one cell is depolarized in an electrical synapse, the joined cell also depolarizes because the ions pass between the cells. Chemical synapses involve the transmission of chemical information from one cell to the next. This section will concentrate on the chemical type of synapse.

An example of a chemical synapse is the neuromuscular junction (NMJ) described in the chapter on muscle tissue. In the nervous system, there are many more synapses that are essentially the same as the NMJ. All synapses have common characteristics, which can be summarized in this list:

- presynaptic element
- neurotransmitter (packaged in vesicles)
- synaptic cleft
- receptor proteins
- postsynaptic element
- neurotransmitter elimination or re-uptake

For the NMJ, these characteristics are as follows: the presynaptic element is the motor neuron's axon terminals, the neurotransmitter is acetylcholine, the synaptic cleft is the space between the cells where the neurotransmitter diffuses, the receptor protein is the nicotinic acetylcholine receptor, the postsynaptic element is the sarcolemma of the muscle cell, and the neurotransmitter is eliminated by acetylcholinesterase. Other synapses are similar to this, and the specifics are different, but they all contain the same characteristics.

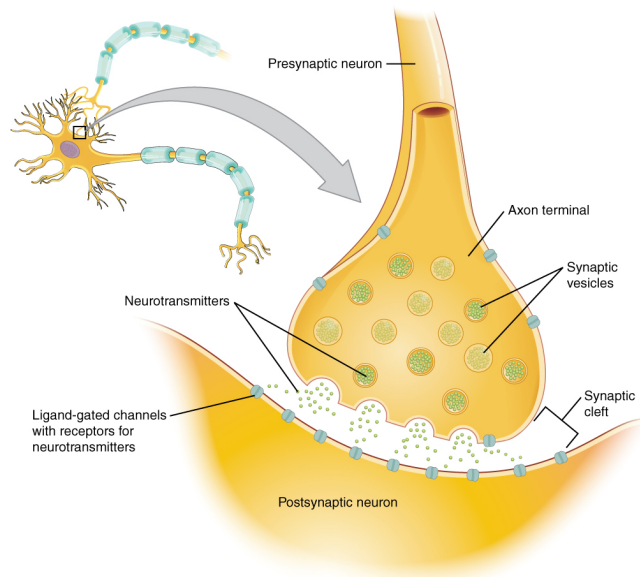
Neurotransmitter Release

When an action potential reaches the axon terminals, voltage-gated Ca^{2+} channels in the membrane of the synaptic end bulb open. The concentration of Ca^{2+} increases inside the end bulb, and the Ca^{2+} ion associates with proteins in the outer surface of neurotransmitter vesicles. The Ca^{2+} facilitates the merging of the vesicle with the

presynaptic membrane so that the neurotransmitter is released through exocytosis into the small gap between the cells, known as the **synaptic cleft**.

Once in the synaptic cleft, the neurotransmitter diffuses the short distance to the postsynaptic membrane and can interact with neurotransmitter receptors. Receptors are specific for the neurotransmitter, and the two fit together like a key and lock. One neurotransmitter binds to its receptor and will not bind to receptors for other neurotransmitters, making the binding a specific chemical event ([\[link\]](#)).

The Synapse



The synapse is a connection between a neuron and its target cell (which is not necessarily a neuron). The presynaptic element is the synaptic end bulb of the axon where Ca^{2+} enters the bulb to cause vesicle fusion and neurotransmitter release. The neurotransmitter diffuses across the synaptic cleft to bind to its receptor. The neurotransmitter is cleared from the synapse either by enzymatic degradation, neuronal reuptake, or glial reuptake.

Neurotransmitter Systems

There are several systems of neurotransmitters that are found at various synapses in the nervous system. These groups refer to the chemicals that are the neurotransmitters, and within the groups are specific systems.

The first group, which is a neurotransmitter system of its own, is the **cholinergic system**. It is the system based on acetylcholine. This includes the NMJ as an example of a cholinergic synapse, but cholinergic synapses are found in other parts of the nervous system. They are in the autonomic nervous system, as well as distributed throughout the brain.

The cholinergic system has two types of receptors, the **nicotinic receptor** is found in the NMJ as well as other synapses. There is also an acetylcholine receptor known as the **muscarinic receptor**. Both of these receptors are named for drugs that interact with the receptor in addition to acetylcholine. Nicotine will bind to the nicotinic receptor and activate it similar to acetylcholine. Muscarine, a product of certain mushrooms, will bind to the

muscarinic receptor. However, nicotine will not bind to the muscarinic receptor and muscarine will not bind to the nicotinic receptor.

Another group of neurotransmitters are amino acids. This includes glutamate (Glu), GABA (gamma-aminobutyric acid, a derivative of glutamate), and glycine (Gly). These amino acids have an amino group and a carboxyl group in their chemical structures. Glutamate is one of the 20 amino acids that are used to make proteins. Each amino acid neurotransmitter would be part of its own system, namely the glutamatergic, GABAergic, and glycinergic systems. They each have their own receptors and do not interact with each other. Amino acid neurotransmitters are eliminated from the synapse by reuptake. A pump in the cell membrane of the presynaptic element, or sometimes a neighboring glial cell, will clear the amino acid from the synaptic cleft so that it can be recycled, repackaged in vesicles, and released again.

Another class of neurotransmitter is the **biogenic amine**, a group of neurotransmitters that are enzymatically made from amino acids. They have amino groups in them, but no longer have carboxyl groups and are therefore no longer classified as amino acids. Serotonin is made from tryptophan. It is the basis of the serotonergic system, which has its own specific receptors. Serotonin is transported back into the presynaptic cell for repackaging.

Other biogenic amines are made from tyrosine, and include dopamine, norepinephrine, and epinephrine. Dopamine is part of its own system, the dopaminergic system, which has dopamine receptors. Dopamine is removed from the synapse by transport proteins in the presynaptic cell membrane. Norepinephrine and epinephrine belong to the adrenergic neurotransmitter system. The two molecules are very similar and bind to the same receptors, which are referred to as alpha and beta receptors. Norepinephrine and epinephrine are also transported back into the presynaptic cell. The chemical epinephrine (epi- = “on”; “-nephrine” = kidney) is also known as adrenaline (renal = “kidney”), and norepinephrine is sometimes referred to as noradrenaline. The adrenal gland produces epinephrine and norepinephrine to be released into the blood stream as hormones.

A **neuropeptide** is a neurotransmitter molecule made up of chains of amino acids connected by peptide bonds. This is what a protein is, but the term protein implies a certain length to the molecule. Some neuropeptides are quite short, such as met-enkephalin, which is five amino acids long. Others are long, such as beta-endorphin, which is 31 amino acids long. Neuropeptides are often released at synapses in combination with another neurotransmitter, and they often act as hormones in other systems of the body, such as vasoactive intestinal peptide (VIP) or substance P.

The effect of a neurotransmitter on the postsynaptic element is entirely dependent on the receptor protein. First, if there is no receptor protein in the membrane of the postsynaptic element, then the neurotransmitter has no effect. The depolarizing or hyperpolarizing effect is also dependent on the receptor. When acetylcholine binds to the nicotinic receptor, the postsynaptic cell is depolarized. This is because the receptor is a cation channel and positively charged Na^+ will rush into the cell. However, when acetylcholine binds to the muscarinic receptor, of which there are several variants, it might cause depolarization or hyperpolarization of the target cell.

The amino acid neurotransmitters, glutamate, glycine, and GABA, are almost exclusively associated with just one effect. Glutamate is considered an excitatory amino acid, but only because Glu receptors in the adult cause depolarization of the postsynaptic cell. Glycine and GABA are considered inhibitory amino acids, again because their receptors cause hyperpolarization.

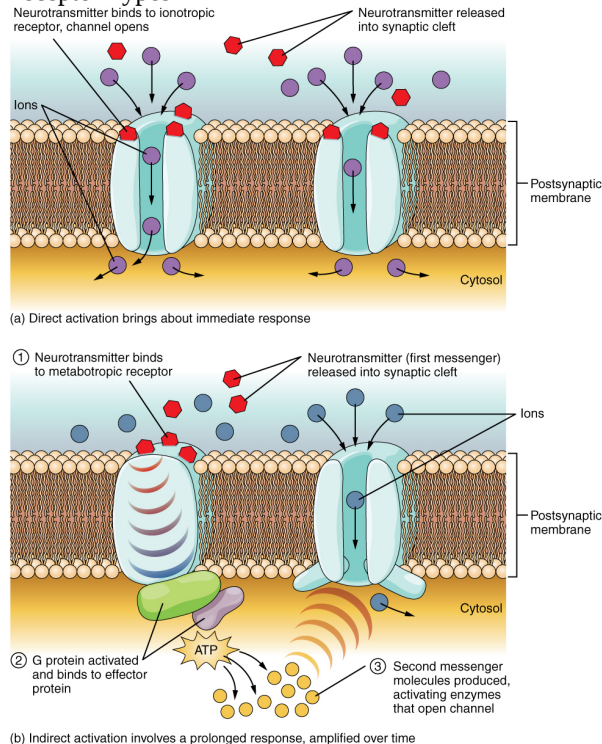
The biogenic amines have mixed effects. For example, the dopamine receptors that are classified as D1 receptors are excitatory whereas D2-type receptors are inhibitory. Biogenic amine receptors and neuropeptide receptors can have even more complex effects because some may not directly affect the membrane potential, but rather have an effect on gene transcription or other metabolic processes in the neuron. The characteristics of the various neurotransmitter systems presented in this section are organized in [\[link\]](#).

The important thing to remember about neurotransmitters, and signaling chemicals in general, is that the effect is entirely dependent on the receptor. Neurotransmitters bind to one of two classes of receptors at the cell surface, ionotropic or metabotropic ([\[link\]](#)). Ionotropic receptors are ligand-gated ion channels, such as the nicotinic receptor for acetylcholine or the glycine receptor. A **metabotropic receptor** involves a complex of proteins that result in metabolic changes within the cell. The receptor complex includes the transmembrane receptor protein, a G protein, and an effector protein. The neurotransmitter, referred to as the first messenger, binds to the receptor

protein on the extracellular surface of the cell, and the intracellular side of the protein initiates activity of the G protein. The **G protein** is a guanosine triphosphate (GTP) hydrolase that physically moves from the receptor protein to the effector protein to activate the latter. An **effector protein** is an enzyme that catalyzes the generation of a new molecule, which acts as the intracellular mediator of the signal that binds to the receptor. This intracellular mediator is called the second messenger.

Different receptors use different second messengers. Two common examples of second messengers are cyclic adenosine monophosphate (cAMP) and inositol triphosphate (IP₃). The enzyme adenylate cyclase (an example of an effector protein) makes cAMP, and phospholipase C is the enzyme that makes IP₃. Second messengers, after they are produced by the effector protein, cause metabolic changes within the cell. These changes are most likely the activation of other enzymes in the cell. In neurons, they often modify ion channels, either opening or closing them. These enzymes can also cause changes in the cell, such as the activation of genes in the nucleus, and therefore the increased synthesis of proteins. In neurons, these kinds of changes are often the basis of stronger connections between cells at the synapse and may be the basis of learning and memory.

Receptor Types



- (a) An ionotropic receptor is a channel that opens when the neurotransmitter binds to it. (b) A metabotropic receptor is a complex that causes metabolic changes in the cell when the neurotransmitter binds to it (1). After binding, the G protein hydrolyzes GTP and moves to the effector protein (2). When the G protein contacts the effector protein, a second messenger is generated, such as cAMP (3). The second messenger can then go on to cause changes in the neuron, such as opening or closing ion channels, metabolic changes, and changes in gene transcription.

Note:

Watch this [video](#) to learn about the release of a neurotransmitter. The action potential reaches the end of the axon, called the axon terminal, and a chemical signal is released to tell the target cell to do something—either to initiate a new action potential, or to suppress that activity. In a very short space, the electrical signal of the action potential is changed into the chemical signal of a neurotransmitter and then back to electrical changes in the target cell membrane. What is the importance of voltage-gated calcium channels in the release of neurotransmitters?

| Characteristics of Neurotransmitter Systems | | | | |
|---|---|---|--|---|
| System | Cholinergic | Amino acids | Biogenic amines | Neuropeptides |
| Neurotransmitters | Acetylcholine | Glutamate, glycine, GABA | Serotonin (5-HT), dopamine, norepinephrine, (epinephrine) | Met-enkephalin, beta-endorphin, VIP, Substance P etc. |
| Receptors | Nicotinic and muscarinic receptors | Glu receptors, gly receptors, GABA receptors | 5-HT receptors, D1 and D2 receptors, α -adrenergic and β -adrenergic receptors | Receptors are too numerous to list, but are specific to the peptides. |
| Elimination | Degradation by acetylcholinesterase | Reuptake by neurons or glia | Reuptake by neurons | Degradation by enzymes called peptidases |
| Postsynaptic effect | Nicotinic receptor causes depolarization. Muscarinic receptors can cause both depolarization or hyperpolarization depending on the subtype. | Glu receptors cause depolarization. Gly and GABA receptors cause hyperpolarization. | Depolarization or hyperpolarization depends on the specific receptor. For example, D1 receptors cause depolarization and D2 receptors cause hyperpolarization. | Depolarization or hyperpolarization depends on the specific receptor. |

Note:

Disorders of the...
Nervous System

The underlying cause of some neurodegenerative diseases, such as Alzheimer's and Parkinson's, appears to be related to proteins—specifically, to proteins behaving badly. One of the strongest theories of what causes Alzheimer's disease is based on the accumulation of beta-amyloid plaques, dense conglomerations of a protein that is not functioning correctly. Parkinson's disease is linked to an increase in a protein known as alpha-synuclein that is toxic to the cells of the substantia nigra nucleus in the midbrain.

For proteins to function correctly, they are dependent on their three-dimensional shape. The linear sequence of amino acids folds into a three-dimensional shape that is based on the interactions between and among those amino acids. When the folding is disturbed, and proteins take on a different shape, they stop functioning correctly. But the disease is not necessarily the result of functional loss of these proteins; rather, these altered proteins start to accumulate and may become toxic. For example, in Alzheimer's, the hallmark of the disease is the accumulation of these amyloid plaques in the cerebral cortex. The term coined to describe this sort of disease is “proteopathy” and it includes other diseases. Creutzfeld-Jacob disease, the human variant of the prion disease known as mad cow disease in the bovine, also involves the accumulation of amyloid plaques, similar to Alzheimer's. Diseases of other organ systems can fall into this group as well, such as cystic fibrosis or type 2 diabetes. Recognizing the relationship between these diseases has suggested new therapeutic possibilities. Interfering with the accumulation of the proteins, and possibly as early as their original production within the cell, may unlock new ways to alleviate these devastating diseases.

Chapter Review

The basis of the electrical signal within a neuron is the action potential that propagates down the axon. For a neuron to generate an action potential, it needs to receive input from another source, either another neuron or a sensory stimulus. That input will result in opening ion channels in the neuron, resulting in a graded potential based on the strength of the stimulus. Graded potentials can be depolarizing or hyperpolarizing and can summate to affect the probability of the neuron reaching threshold.

Graded potentials can be the result of sensory stimuli. If the sensory stimulus is received by the dendrites of a unipolar sensory neuron, such as the sensory neuron ending in the skin, the graded potential is called a generator potential because it can directly generate the action potential in the initial segment of the axon. If the sensory stimulus is received by a specialized sensory receptor cell, the graded potential is called a receptor potential. Graded potentials produced by interactions between neurons at synapses are called postsynaptic potentials (PSPs). A depolarizing graded potential at a synapse is called an excitatory PSP, and a hyperpolarizing graded potential at a synapse is called an inhibitory PSP.

Synapses are the contacts between neurons, which can either be chemical or electrical in nature. Chemical synapses are far more common. At a chemical synapse, neurotransmitter is released from the presynaptic element and diffuses across the synaptic cleft. The neurotransmitter binds to a receptor protein and causes a change in the postsynaptic membrane (the PSP). The neurotransmitter must be inactivated or removed from the synaptic cleft so that the stimulus is limited in time.

The particular characteristics of a synapse vary based on the neurotransmitter system produced by that neuron. The cholinergic system is found at the neuromuscular junction and in certain places within the nervous system. Amino acids, such as glutamate, glycine, and gamma-aminobutyric acid (GABA) are used as neurotransmitters. Other neurotransmitters are the result of amino acids being enzymatically changed, as in the biogenic amines, or being covalently bonded together, as in the neuropeptides.

Interactive Link Questions

Exercise:

Problem:

Watch this [video](#) to learn about summation. The process of converting electrical signals to chemical signals and back requires subtle changes that can result in transient increases or decreases in membrane voltage. To cause a lasting change in the target cell, multiple signals are usually added together, or summated. Does spatial summation have to happen all at once, or can the separate signals arrive on the postsynaptic neuron at slightly different times? Explain your answer.

Solution:

A second signal from a separate presynaptic neuron can arrive slightly later, as long as it arrives before the first one dies off, or dissipates.

Exercise:**Problem:**

Watch this [video](#) to learn about the release of a neurotransmitter. The action potential reaches the end of the axon, called the axon terminal, and a chemical signal is released to tell the target cell to do something, either initiate a new action potential, or to suppress that activity. In a very short space, the electrical signal of the action potential is changed into the chemical signal of a neurotransmitter, and then back to electrical changes in the target cell membrane. What is the importance of voltage-gated calcium channels in the release of neurotransmitters?

Solution:

The action potential depolarizes the cell membrane of the axon terminal, which contains the voltage-gated Ca^{2+} channel. That voltage change opens the channel so that Ca^{2+} can enter the axon terminal. Calcium ions make it possible for synaptic vesicles to release their contents through exocytosis.

Review Questions**Exercise:****Problem:**

How much of a change in the membrane potential is necessary for the summation of postsynaptic potentials to result in an action potential being generated?

- a. +30 mV
 - b. +15 mV
 - c. +10 mV
 - d. -15 mV
-

Solution:

B

Exercise:**Problem:**

A channel opens on a postsynaptic membrane that causes a negative ion to enter the cell. What type of graded potential is this?

- a. depolarizing
- b. repolarizing
- c. hyperpolarizing

d. non-polarizing

Solution:

C

Exercise:

Problem: What neurotransmitter is released at the neuromuscular junction?

- a. norepinephrine
- b. serotonin
- c. dopamine
- d. acetylcholine

Solution:

D

Exercise:

Problem: What type of receptor requires an effector protein to initiate a signal?

- a. biogenic amine
- b. ionotropic receptor
- c. cholinergic system
- d. metabotropic receptor

Solution:

D

Exercise:

Problem: Which of the following neurotransmitters is associated with inhibition exclusively?

- a. GABA
- b. acetylcholine
- c. glutamate
- d. norepinephrine

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

If a postsynaptic cell has synapses from five different cells, and three cause EPSPs and two of them cause IPSPs, give an example of a series of depolarizations and hyperpolarizations that would result in the neuron reaching threshold.

Solution:

EPSP1 = +5 mV, EPSP2 = +7 mV, EPSP 3 = +10 mV, IPSP1 = -4 mV, IPSP2 = -3 mV. $5 + 7 + 10 - 4 - 3 = +15$ mV.

Exercise:**Problem:**

Why is the receptor the important element determining the effect a neurotransmitter has on a target cell?

Solution:

Different neurotransmitters have different receptors. Thus, the type of receptor in the postsynaptic cell is what determines which ion channels open. Acetylcholine binding to the nicotinic receptor causes cations to cross the membrane. GABA binding to its receptor causes the anion chloride to cross the membrane.

Glossary**biogenic amine**

class of neurotransmitters that are enzymatically derived from amino acids but no longer contain a carboxyl group

chemical synapse

connection between two neurons, or between a neuron and its target, where a neurotransmitter diffuses across a very short distance

cholinergic system

neurotransmitter system of acetylcholine, which includes its receptors and the enzyme acetylcholinesterase

effector protein

enzyme that catalyzes the generation of a new molecule, which acts as the intracellular mediator of the signal that binds to the receptor

electrical synapse

connection between two neurons, or any two electrically active cells, where ions flow directly through channels spanning their adjacent cell membranes

excitatory postsynaptic potential (EPSP)

graded potential in the postsynaptic membrane that is the result of depolarization and makes an action potential more likely to occur

generator potential

graded potential from dendrites of a unipolar cell which generates the action potential in the initial segment of that cell's axon

G protein

guanosine triphosphate (GTP) hydrolase that physically moves from the receptor protein to the effector protein to activate the latter

inhibitory postsynaptic potential (IPSP)

graded potential in the postsynaptic membrane that is the result of hyperpolarization and makes an action potential less likely to occur

metabotropic receptor

neurotransmitter receptor that involves a complex of proteins that cause metabolic changes in a cell

muscarinic receptor

type of acetylcholine receptor protein that is characterized by also binding to muscarine and is a metabotropic receptor

neuropeptide

neurotransmitter type that includes protein molecules and shorter chains of amino acids

nicotinic receptor

type of acetylcholine receptor protein that is characterized by also binding to nicotine and is an ionotropic receptor

postsynaptic potential (PSP)

graded potential in the postsynaptic membrane caused by the binding of neurotransmitter to protein receptors

receptor potential

graded potential in a specialized sensory cell that directly causes the release of neurotransmitter without an intervening action potential

spatial summation

combination of graded potentials across the neuronal cell membrane caused by signals from separate presynaptic elements that add up to initiate an action potential

summate

to add together, as in the cumulative change in postsynaptic potentials toward reaching threshold in the membrane, either across a span of the membrane or over a certain amount of time

synaptic cleft

small gap between cells in a chemical synapse where neurotransmitter diffuses from the presynaptic element to the postsynaptic element

temporal summation

combination of graded potentials at the same location on a neuron resulting in a strong signal from one input

Introduction

class="introduction"

Human Nervous System

The
ability to
balance
like an
acrobat
combines
functions
throughou
t the
nervous
system.

The
central
and
peripheral
divisions
coordinate
control of
the body
using the
senses of
balance,
body
position,
and touch
on the
soles of
the feet.

(credit:
Rhett
Sutphin)



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Relate the developmental processes of the embryonic nervous system to the adult structures
- Name the major regions of the adult nervous system
- Locate regions of the cerebral cortex on the basis of anatomical landmarks common to all human brains
- Describe the regions of the spinal cord in cross-section
- List the cranial nerves in order of anatomical location and provide the central and peripheral connections
- List the spinal nerves by vertebral region and by which nerve plexus each supplies

The nervous system is responsible for controlling much of the body, both through somatic (voluntary) and autonomic (involuntary) functions. The structures of the nervous system must be described in detail to understand how many of these functions are possible. There is a physiological concept known as localization of function that states that certain structures are specifically responsible for prescribed functions. It is an underlying concept in all of anatomy and physiology, but the nervous system illustrates the concept very well.

Fresh, unstained nervous tissue can be described as gray or white matter, and within those two types of tissue it can be very hard to see any detail. However, as specific regions and structures have been described, they were related to specific functions. Understanding these structures and the functions they perform requires a detailed description of the anatomy of the nervous system, delving deep into what the central and peripheral structures are.

The place to start this study of the nervous system is the beginning of the individual human life, within the womb. The embryonic development of the nervous system allows for a simple framework on which progressively more complicated structures can be built. With this framework in place, a thorough investigation of the nervous system is possible.

The Central Nervous System

By the end of this section, you will be able to:

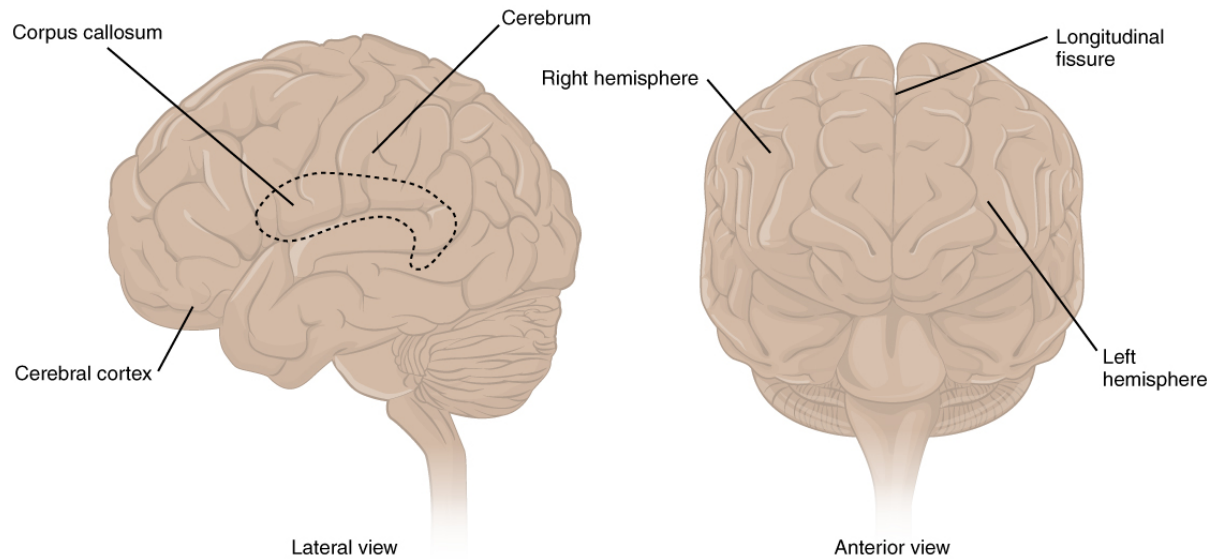
- Name the major regions of the adult brain
- Describe the connections between the cerebrum and brain stem through the diencephalon, and from those regions into the spinal cord
- Recognize the complex connections within the subcortical structures of the basal nuclei
- Explain the arrangement of gray and white matter in the spinal cord

The brain and the spinal cord are the central nervous system, and they represent the main organs of the nervous system. The spinal cord is a single structure, whereas the adult brain is described in terms of four major regions: the cerebrum, the diencephalon, the brain stem, and the cerebellum. A person's conscious experiences are based on neural activity in the brain. The regulation of homeostasis is governed by a specialized region in the brain. The coordination of reflexes depends on the integration of sensory and motor pathways in the spinal cord.

The Cerebrum

The iconic gray mantle of the human brain, which appears to make up most of the mass of the brain, is the **cerebrum** ([\[link\]](#)). The wrinkled portion is the **cerebral cortex**, and the rest of the structure is beneath that outer covering. There is a large separation between the two sides of the cerebrum called the **longitudinal fissure**. It separates the cerebrum into two distinct halves, a right and left **cerebral hemisphere**. Deep within the cerebrum, the white matter of the **corpus callosum** provides the major pathway for communication between the two hemispheres of the cerebral cortex.

The Cerebrum



The cerebrum is a large component of the CNS in humans, and the most obvious aspect of it is the folded surface called the cerebral cortex.

Many of the higher neurological functions, such as memory, emotion, and consciousness, are the result of cerebral function. The complexity of the cerebrum is different across vertebrate species. The cerebrum of the most primitive vertebrates is not much more than the connection for the sense of smell. In mammals, the cerebrum comprises the outer gray matter that is the cortex (from the Latin word meaning “bark of a tree”) and several deep nuclei that belong to three important functional groups. The **basal nuclei** are responsible for cognitive processing, the most important function being that associated with planning movements. The **basal forebrain** contains nuclei that are important in learning and memory. The **limbic cortex** is the region of the cerebral cortex that is part of the **limbic system**, a collection of structures involved in emotion, memory, and behavior.

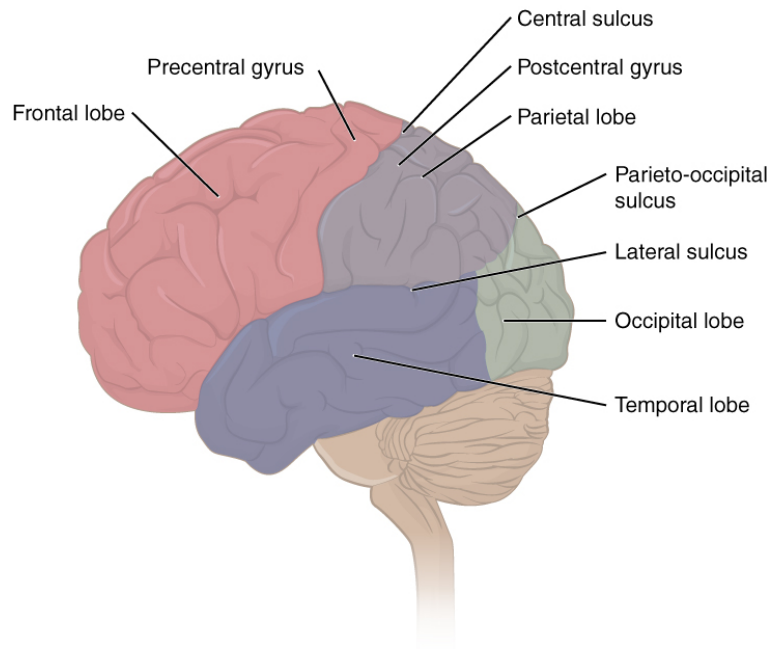
Cerebral Cortex

The cerebrum is covered by a continuous layer of gray matter that wraps around either side of the forebrain—the cerebral cortex. This thin, extensive region of wrinkled gray matter is responsible for the higher functions of the nervous system. A **gyrus** (plural = gyri) is the ridge of one of those wrinkles, and a **sulcus** (plural = sulci) is the groove between two gyri. The pattern of these folds of tissue indicates specific regions of the cerebral cortex.

The head is limited by the size of the birth canal, and the brain must fit inside the cranial cavity of the skull. Extensive folding in the cerebral cortex enables more gray matter to fit into this limited space. If the gray matter of the cortex were peeled off of the cerebrum and laid out flat, its surface area would be roughly equal to one square meter.

The folding of the cortex maximizes the amount of gray matter in the cranial cavity. During embryonic development, as the telencephalon expands within the skull, the brain goes through a regular course of growth that results in everyone's brain having a similar pattern of folds. The surface of the brain can be mapped on the basis of the locations of large gyri and sulci. Using these landmarks, the cortex can be separated into four major regions, or lobes ([\[link\]](#)). The **lateral sulcus** that separates the **temporal lobe** from the other regions is one such landmark. Superior to the lateral sulcus are the **parietal lobe** and **frontal lobe**, which are separated from each other by the **central sulcus**. The posterior region of the cortex is the **occipital lobe**, which has no obvious anatomical border between it and the parietal or temporal lobes on the lateral surface of the brain. From the medial surface, an obvious landmark separating the parietal and occipital lobes is called the **parieto-occipital sulcus**. The fact that there is no obvious anatomical border between these lobes is consistent with the functions of these regions being interrelated.

Lobes of the Cerebral Cortex



The cerebral cortex is divided into four lobes. Extensive folding increases the surface area available for cerebral functions.

Different regions of the cerebral cortex can be associated with particular functions, a concept known as localization of function. In the early 1900s, a German neuroscientist named Korbinian Brodmann performed an extensive study of the microscopic anatomy—the cytoarchitecture—of the cerebral cortex and divided the cortex into 52 separate regions on the basis of the histology of the cortex. His work resulted in a system of classification known as **Brodmann's areas**, which is still used today to describe the anatomical distinctions within the cortex ([\[link\]](#)). The results from Brodmann's work on the anatomy align very well with the functional differences within the cortex. Areas 17 and 18 in the occipital lobe are responsible for primary visual perception. That visual information is complex, so it is processed in the temporal and parietal lobes as well.

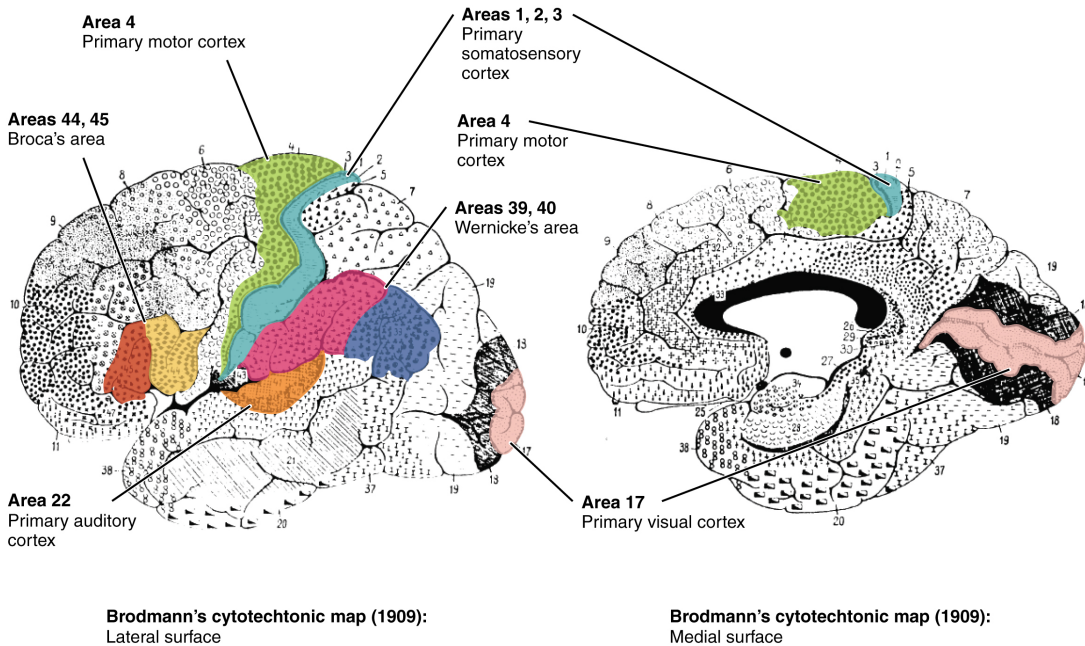
The temporal lobe is associated with primary auditory sensation, known as Brodmann's areas 41 and 42 in the superior temporal lobe. Because regions

of the temporal lobe are part of the limbic system, memory is an important function associated with that lobe. Memory is essentially a sensory function; memories are recalled sensations such as the smell of Mom's baking or the sound of a barking dog. Even memories of movement are really the memory of sensory feedback from those movements, such as stretching muscles or the movement of the skin around a joint. Structures in the temporal lobe are responsible for establishing long-term memory, but the ultimate location of those memories is usually in the region in which the sensory perception was processed.

The main sensation associated with the parietal lobe is **somatosensation**, meaning the general sensations associated with the body. Posterior to the central sulcus is the **postcentral gyrus**, the primary somatosensory cortex, which is identified as Brodmann's areas 1, 2, and 3. All of the tactile senses are processed in this area, including touch, pressure, tickle, pain, itch, and vibration, as well as more general senses of the body such as **proprioception** and **kinesthesia**, which are the senses of body position and movement, respectively.

Anterior to the central sulcus is the frontal lobe, which is primarily associated with motor functions. The **precentral gyrus** is the primary motor cortex. Cells from this region of the cerebral cortex are the upper motor neurons that instruct cells in the spinal cord to move skeletal muscles. Anterior to this region are a few areas that are associated with planned movements. The **premotor area** is responsible for thinking of a movement to be made. The **frontal eye fields** are important in eliciting eye movements and in attending to visual stimuli. **Broca's area** is responsible for the production of language, or controlling movements responsible for speech; in the vast majority of people, it is located only on the left side. Anterior to these regions is the **prefrontal lobe**, which serves cognitive functions that can be the basis of personality, short-term memory, and consciousness. The prefrontal lobotomy is an outdated mode of treatment for personality disorders (psychiatric conditions) that profoundly affected the personality of the patient.

Brodmann's Areas of the Cerebral Cortex



Brodman mapping of functionally distinct regions of the cortex was based on its cytoarchitecture at a microscopic level.

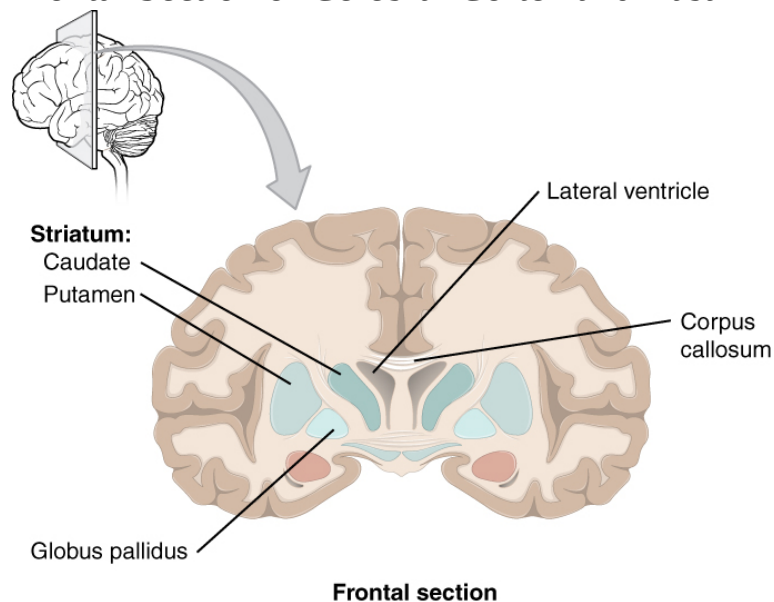
Subcortical structures

Beneath the cerebral cortex are sets of nuclei known as **subcortical nuclei** that augment cortical processes. The nuclei of the basal forebrain serve as the primary location for acetylcholine production, which modulates the overall activity of the cortex, possibly leading to greater attention to sensory stimuli. Alzheimer's disease is associated with a loss of neurons in the basal forebrain. The **hippocampus** and **amygdala** are medial-lobe structures that, along with the adjacent cortex, are involved in long-term memory formation and emotional responses. The basal nuclei are a set of nuclei in the cerebrum responsible for comparing cortical processing with the general state of activity in the nervous system to influence the likelihood of movement taking place. For example, while a student is sitting in a classroom listening to a lecture, the basal nuclei will keep the urge to jump up and scream from actually happening. (The basal nuclei are also referred

to as the basal ganglia, although that is potentially confusing because the term ganglia is typically used for peripheral structures.)

The major structures of the basal nuclei that control movement are the **caudate**, **putamen**, and **globus pallidus**, which are located deep in the cerebrum. The caudate is a long nucleus that follows the basic C-shape of the cerebrum from the frontal lobe, through the parietal and occipital lobes, into the temporal lobe. The putamen is mostly deep in the anterior regions of the frontal and parietal lobes. Together, the caudate and putamen are called the **striatum**. The globus pallidus is a layered nucleus that lies just medial to the putamen; they are called the lenticular nuclei because they look like curved pieces fitting together like lenses. The globus pallidus has two subdivisions, the external and internal segments, which are lateral and medial, respectively. These nuclei are depicted in a frontal section of the brain in [\[link\]](#).

Frontal Section of Cerebral Cortex and Basal Nuclei

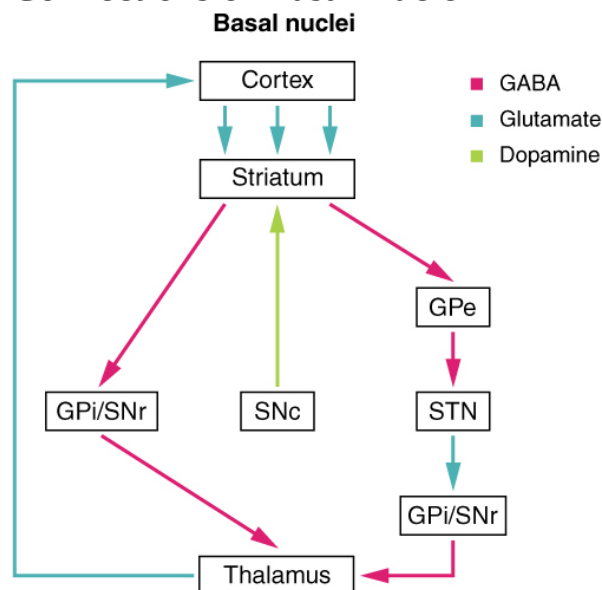


The major components of the basal nuclei, shown in a frontal section of the brain, are the caudate (just lateral to the lateral ventricle), the putamen (inferior to the caudate and separated by the large white-matter structure called the internal

capsule), and the globus pallidus (medial to the putamen).

The basal nuclei in the cerebrum are connected with a few more nuclei in the brain stem that together act as a functional group that forms a motor pathway. Two streams of information processing take place in the basal nuclei. All input to the basal nuclei is from the cortex into the striatum ([\[link\]](#)). The **direct pathway** is the projection of axons from the striatum to the globus pallidus internal segment (GPi) and the **substantia nigra pars reticulata** (SNr). The GPi/SNr then projects to the thalamus, which projects back to the cortex. The **indirect pathway** is the projection of axons from the striatum to the globus pallidus external segment (GPe), then to the subthalamic nucleus (STN), and finally to GPi/SNr. The two streams both target the GPi/SNr, but one has a direct projection and the other goes through a few intervening nuclei. The direct pathway causes the **disinhibition** of the thalamus (inhibition of one cell on a target cell that then inhibits the first cell), whereas the indirect pathway causes, or reinforces, the normal inhibition of the thalamus. The thalamus then can either excite the cortex (as a result of the direct pathway) or fail to excite the cortex (as a result of the indirect pathway).

Connections of Basal Nuclei



Input to the basal nuclei is from the cerebral cortex, which is an

excitatory connection releasing glutamate as a neurotransmitter. This input is to the striatum, or the caudate and putamen. In the direct pathway, the striatum projects to the internal segment of the globus pallidus and the substantia nigra pars reticulata (GPi/SNr). This is an inhibitory pathway, in which GABA is released at the synapse, and the target cells are hyperpolarized and less likely to fire. The output from the basal nuclei is to the thalamus, which is an inhibitory projection using GABA.

The switch between the two pathways is the **substantia nigra pars compacta**, which projects to the striatum and releases the neurotransmitter dopamine. Dopamine receptors are either excitatory (D1-type receptors) or inhibitory (D2-type receptors). The direct pathway is activated by dopamine, and the indirect pathway is inhibited by dopamine. When the substantia nigra pars compacta is firing, it signals to the basal nuclei that the body is in an active state, and movement will be more likely. When the substantia nigra pars compacta is silent, the body is in a passive state, and movement is inhibited. To illustrate this situation, while a student is sitting listening to a lecture, the substantia nigra pars compacta would be silent and the student less likely to get up and walk around. Likewise, while the professor is lecturing, and walking around at the front of the classroom, the professor's substantia nigra pars compacta would be active, in keeping with his or her activity level.

Note:



Watch this [video](#) to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the direct pathway is the shorter pathway through the system that results in increased activity in the cerebral cortex and increased motor activity. The direct pathway is described as resulting in “disinhibition” of the thalamus. What does disinhibition mean? What are the two neurons doing individually to cause this?

Note:



Watch this [video](#) to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the indirect pathway is the longer pathway through the system that results in decreased activity in the cerebral cortex, and therefore less motor activity. The indirect pathway has an extra couple of connections in it, including disinhibition of the subthalamic nucleus. What is the end result on the thalamus, and therefore on movement initiated by the cerebral cortex?

Note:**Everyday Connections****The Myth of Left Brain/Right Brain**

There is a persistent myth that people are “right-brained” or “left-brained,” which is an oversimplification of an important concept about the cerebral hemispheres. There is some lateralization of function, in which the left side of the brain is devoted to language function and the right side is devoted to spatial and nonverbal reasoning. Whereas these functions are predominantly associated with those sides of the brain, there is no monopoly by either side on these functions. Many pervasive functions, such as language, are distributed globally around the cerebrum.

Some of the support for this misconception has come from studies of split brains. A drastic way to deal with a rare and devastating neurological condition (intractable epilepsy) is to separate the two hemispheres of the brain. After sectioning the corpus callosum, a split-brained patient will have trouble producing verbal responses on the basis of sensory information processed on the right side of the cerebrum, leading to the idea that the left side is responsible for language function.

However, there are well-documented cases of language functions lost from damage to the right side of the brain. The deficits seen in damage to the left side of the brain are classified as aphasia, a loss of speech function; damage on the right side can affect the use of language. Right-side damage can result in a loss of ability to understand figurative aspects of speech, such as jokes, irony, or metaphors. Nonverbal aspects of speech can be affected by damage to the right side, such as facial expression or body language, and right-side damage can lead to a “flat affect” in speech, or a loss of emotional expression in speech—sounding like a robot when talking.

The Diencephalon

The diencephalon is the one region of the adult brain that retains its name from embryologic development. The etymology of the word diencephalon translates to “through brain.” It is the connection between the cerebrum and the rest of the nervous system, with one exception. The rest of the brain, the

spinal cord, and the PNS all send information to the cerebrum through the diencephalon. Output from the cerebrum passes through the diencephalon. The single exception is the system associated with **olfaction**, or the sense of smell, which connects directly with the cerebrum. In the earliest vertebrate species, the cerebrum was not much more than olfactory bulbs that received peripheral information about the chemical environment (to call it smell in these organisms is imprecise because they lived in the ocean).

The diencephalon is deep beneath the cerebrum and constitutes the walls of the third ventricle. The diencephalon can be described as any region of the brain with “thalamus” in its name. The two major regions of the diencephalon are the thalamus itself and the hypothalamus ([\[link\]](#)). There are other structures, such as the **epithalamus**, which contains the pineal gland, or the **subthalamus**, which includes the subthalamic nucleus that is part of the basal nuclei.

Thalamus

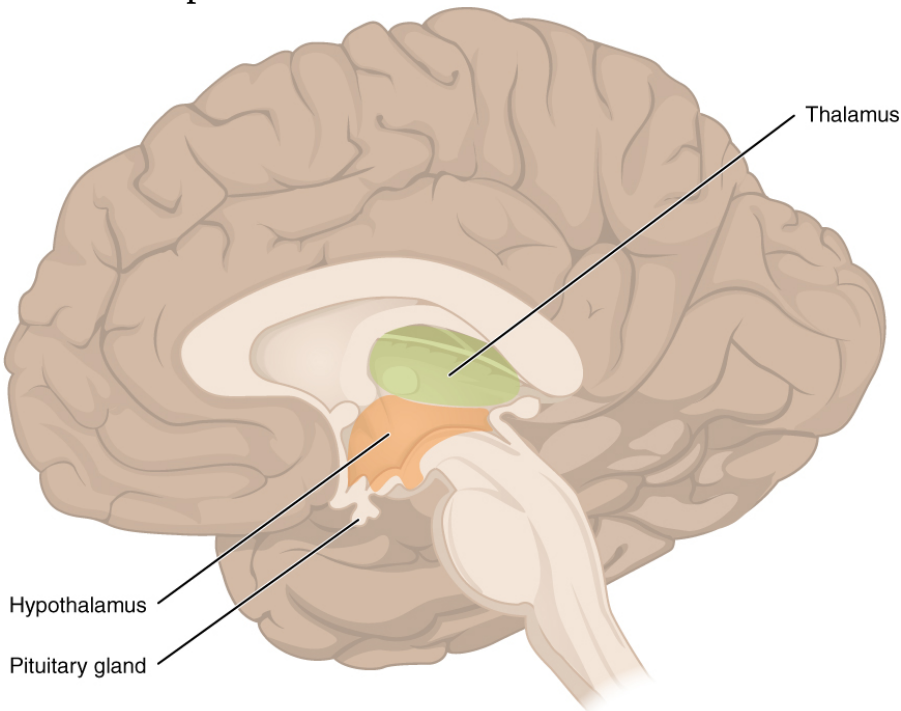
The **thalamus** is a collection of nuclei that relay information between the cerebral cortex and the periphery, spinal cord, or brain stem. All sensory information, except for the sense of smell, passes through the thalamus before processing by the cortex. Axons from the peripheral sensory organs, or intermediate nuclei, synapse in the thalamus, and thalamic neurons project directly to the cerebrum. It is a requisite synapse in any sensory pathway, except for olfaction. The thalamus does not just pass the information on, it also processes that information. For example, the portion of the thalamus that receives visual information will influence what visual stimuli are important, or what receives attention.

The cerebrum also sends information down to the thalamus, which usually communicates motor commands. This involves interactions with the cerebellum and other nuclei in the brain stem. The cerebrum interacts with the basal nuclei, which involves connections with the thalamus. The primary output of the basal nuclei is to the thalamus, which relays that output to the cerebral cortex. The cortex also sends information to the thalamus that will then influence the effects of the basal nuclei.

Hypothalamus

Inferior and slightly anterior to the thalamus is the **hypothalamus**, the other major region of the diencephalon. The hypothalamus is a collection of nuclei that are largely involved in regulating homeostasis. The hypothalamus is the executive region in charge of the autonomic nervous system and the endocrine system through its regulation of the anterior pituitary gland. Other parts of the hypothalamus are involved in memory and emotion as part of the limbic system.

The Diencephalon



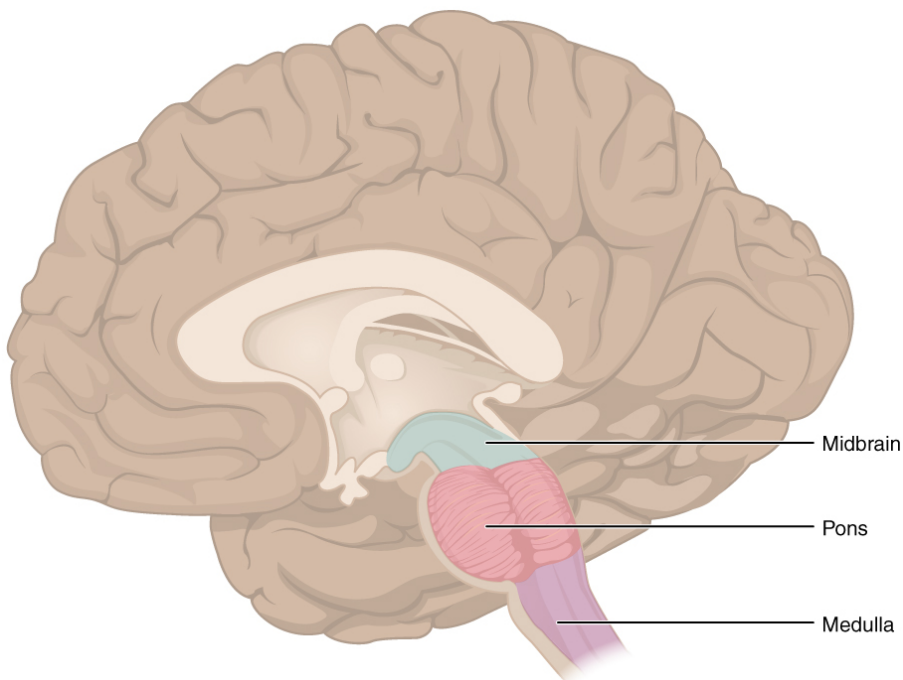
The diencephalon is composed primarily of the thalamus and hypothalamus, which together define the walls of the third ventricle. The thalami are two elongated, ovoid structures on either side of the midline that make contact in the middle. The hypothalamus is inferior and anterior to the thalamus, culminating in a sharp angle to which the pituitary gland is attached.

Brain Stem

The midbrain and hindbrain (composed of the pons and the medulla) are collectively referred to as the brain stem ([link](#)). The structure emerges from the ventral surface of the forebrain as a tapering cone that connects the brain to the spinal cord. Attached to the brain stem, but considered a separate region of the adult brain, is the cerebellum. The midbrain coordinates sensory representations of the visual, auditory, and somatosensory perceptual spaces. The pons is the main connection with the cerebellum. The pons and the medulla regulate several crucial functions, including the cardiovascular and respiratory systems and rates.

The cranial nerves connect through the brain stem and provide the brain with the sensory input and motor output associated with the head and neck, including most of the special senses. The major ascending and descending pathways between the spinal cord and brain, specifically the cerebrum, pass through the brain stem.

The Brain Stem



The brain stem comprises three regions: the midbrain, the pons, and the medulla.

Midbrain

One of the original regions of the embryonic brain, the midbrain is a small region between the thalamus and pons. It is separated into the **tectum** and **tegmentum**, from the Latin words for roof and floor, respectively. The cerebral aqueduct passes through the center of the midbrain, such that these regions are the roof and floor of that canal.

The tectum is composed of four bumps known as the colliculi (singular = colliculus), which means “little hill” in Latin. The **inferior colliculus** is the inferior pair of these enlargements and is part of the auditory brain stem pathway. Neurons of the inferior colliculus project to the thalamus, which then sends auditory information to the cerebrum for the conscious perception of sound. The **superior colliculus** is the superior pair and combines sensory information about visual space, auditory space, and somatosensory space. Activity in the superior colliculus is related to orienting the eyes to a sound or touch stimulus. If you are walking along the sidewalk on campus and you hear chirping, the superior colliculus coordinates that information with your awareness of the visual location of the tree right above you. That is the correlation of auditory and visual maps. If you suddenly feel something wet fall on your head, your superior colliculus integrates that with the auditory and visual maps and you know that the chirping bird just relieved itself on you. You want to look up to see the culprit, but do not.

The tegmentum is continuous with the gray matter of the rest of the brain stem. Throughout the midbrain, pons, and medulla, the tegmentum contains the nuclei that receive and send information through the cranial nerves, as well as regions that regulate important functions such as those of the cardiovascular and respiratory systems.

Pons

The word pons comes from the Latin word for bridge. It is visible on the anterior surface of the brain stem as the thick bundle of white matter attached to the cerebellum. The pons is the main connection between the cerebellum and the brain stem. The bridge-like white matter is only the anterior surface of the pons; the gray matter beneath that is a continuation of the tegmentum from the midbrain. Gray matter in the tegmentum region of the pons contains neurons receiving descending input from the forebrain that is sent to the cerebellum.

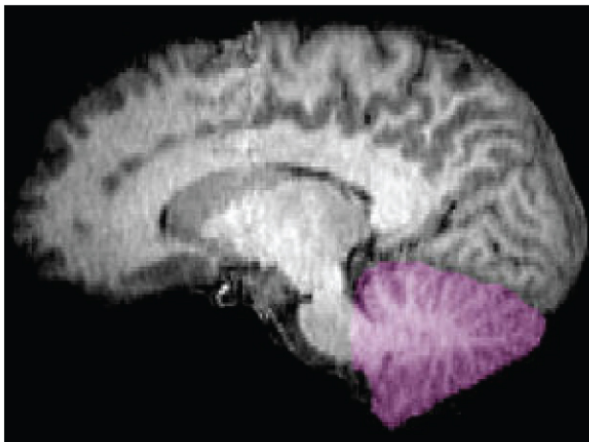
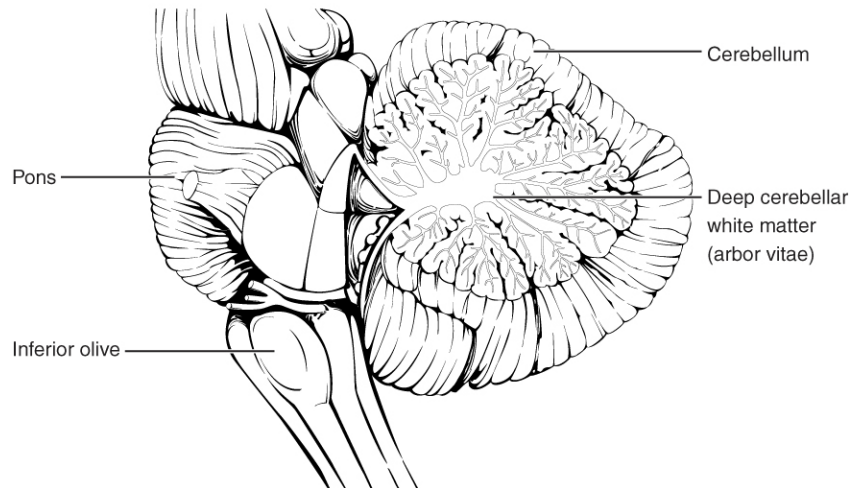
Medulla

The medulla is the region known as the myelencephalon in the embryonic brain. The initial portion of the name, “myel,” refers to the significant white matter found in this region—especially on its exterior, which is continuous with the white matter of the spinal cord. The tegmentum of the midbrain and pons continues into the medulla because this gray matter is responsible for processing cranial nerve information. A diffuse region of gray matter throughout the brain stem, known as the **reticular formation**, is related to sleep and wakefulness, such as general brain activity and attention.

The Cerebellum

The **cerebellum**, as the name suggests, is the “little brain.” It is covered in gyri and sulci like the cerebrum, and looks like a miniature version of that part of the brain ([\[link\]](#)). The cerebellum is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord. It accounts for approximately 10 percent of the mass of the brain.

The Cerebellum



The cerebellum is situated on the posterior surface of the brain stem. Descending input from the cerebellum enters through the large white matter structure of the pons. Ascending input from the periphery and spinal cord enters through the fibers of the inferior olive. Output goes to the midbrain, which sends a descending signal to the spinal cord.

Descending fibers from the cerebrum have branches that connect to neurons in the pons. Those neurons project into the cerebellum, providing a copy of

motor commands sent to the spinal cord. Sensory information from the periphery, which enters through spinal or cranial nerves, is copied to a nucleus in the medulla known as the **inferior olive**. Fibers from this nucleus enter the cerebellum and are compared with the descending commands from the cerebrum. If the primary motor cortex of the frontal lobe sends a command down to the spinal cord to initiate walking, a copy of that instruction is sent to the cerebellum. Sensory feedback from the muscles and joints, proprioceptive information about the movements of walking, and sensations of balance are sent to the cerebellum through the inferior olive and the cerebellum compares them. If walking is not coordinated, perhaps because the ground is uneven or a strong wind is blowing, then the cerebellum sends out a corrective command to compensate for the difference between the original cortical command and the sensory feedback. The output of the cerebellum is into the midbrain, which then sends a descending input to the spinal cord to correct the messages going to skeletal muscles.

The Spinal Cord

The description of the CNS is concentrated on the structures of the brain, but the spinal cord is another major organ of the system. Whereas the brain develops out of expansions of the neural tube into primary and then secondary vesicles, the spinal cord maintains the tube structure and is only specialized into certain regions. As the spinal cord continues to develop in the newborn, anatomical features mark its surface. The anterior midline is marked by the **anterior median fissure**, and the posterior midline is marked by the **posterior median sulcus**. Axons enter the posterior side through the **dorsal (posterior) nerve root**, which marks the **posterolateral sulcus** on either side. The axons emerging from the anterior side do so through the **ventral (anterior) nerve root**. Note that it is common to see the terms dorsal (dorsal = “back”) and ventral (ventral = “belly”) used interchangeably with posterior and anterior, particularly in reference to nerves and the structures of the spinal cord. You should learn to be comfortable with both.

On the whole, the posterior regions are responsible for sensory functions and the anterior regions are associated with motor functions. This comes

from the initial development of the spinal cord, which is divided into the **basal plate** and the **alar plate**. The basal plate is closest to the ventral midline of the neural tube, which will become the anterior face of the spinal cord and gives rise to motor neurons. The alar plate is on the dorsal side of the neural tube and gives rise to neurons that will receive sensory input from the periphery.

The length of the spinal cord is divided into regions that correspond to the regions of the vertebral column. The name of a spinal cord region corresponds to the level at which spinal nerves pass through the intervertebral foramina. Immediately adjacent to the brain stem is the cervical region, followed by the thoracic, then the lumbar, and finally the sacral region. The spinal cord is not the full length of the vertebral column because the spinal cord does not grow significantly longer after the first or second year, but the skeleton continues to grow. The nerves that emerge from the spinal cord pass through the intervertebral foramina at the respective levels. As the vertebral column grows, these nerves grow with it and result in a long bundle of nerves that resembles a horse's tail and is named the **cauda equina**. The sacral spinal cord is at the level of the upper lumbar vertebral bones. The spinal nerves extend from their various levels to the proper level of the vertebral column.

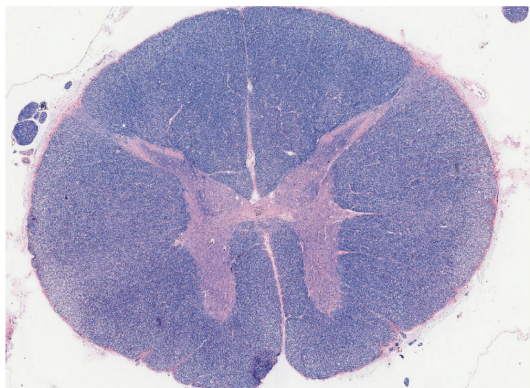
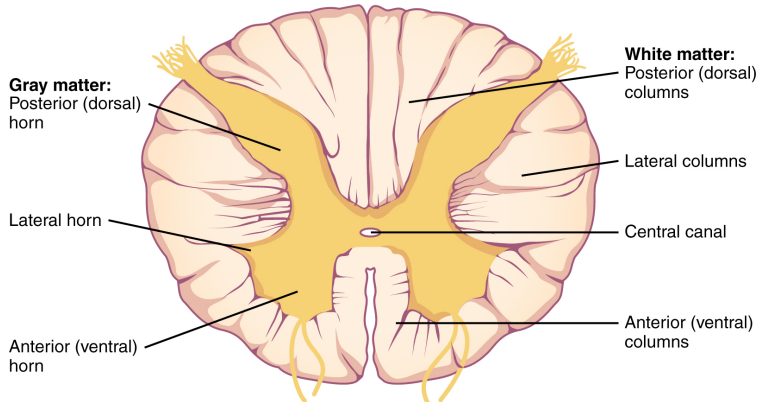
Gray Horns

In cross-section, the gray matter of the spinal cord has the appearance of an ink-blot test, with the spread of the gray matter on one side replicated on the other—a shape reminiscent of a bulbous capital “H.” As shown in [\[link\]](#), the gray matter is subdivided into regions that are referred to as horns. The **posterior horn** is responsible for sensory processing. The **anterior horn** sends out motor signals to the skeletal muscles. The **lateral horn**, which is only found in the thoracic, upper lumbar, and sacral regions, is the central component of the sympathetic division of the autonomic nervous system.

Some of the largest neurons of the spinal cord are the multipolar motor neurons in the anterior horn. The fibers that cause contraction of skeletal muscles are the axons of these neurons. The motor neuron that causes

contraction of the big toe, for example, is located in the sacral spinal cord. The axon that has to reach all the way to the belly of that muscle may be a meter in length. The neuronal cell body that maintains that long fiber must be quite large, possibly several hundred micrometers in diameter, making it one of the largest cells in the body.

Cross-section of Spinal Cord



The cross-section of a thoracic spinal cord segment shows the posterior, anterior, and lateral horns of gray matter, as well as the posterior, anterior, and lateral columns of white matter. LM $\times 40$. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

White Columns

Just as the gray matter is separated into horns, the white matter of the spinal cord is separated into columns. **Ascending tracts** of nervous system fibers in these columns carry sensory information up to the brain, whereas **descending tracts** carry motor commands from the brain. Looking at the spinal cord longitudinally, the columns extend along its length as continuous bands of white matter. Between the two posterior horns of gray matter are the **posterior columns**. Between the two anterior horns, and bounded by the axons of motor neurons emerging from that gray matter area, are the **anterior columns**. The white matter on either side of the spinal cord, between the posterior horn and the axons of the anterior horn neurons, are the **lateral columns**. The posterior columns are composed of axons of ascending tracts. The anterior and lateral columns are composed of many different groups of axons of both ascending and descending tracts—the latter carrying motor commands down from the brain to the spinal cord to control output to the periphery.

Note:



Watch this [video](#) to learn about the gray matter of the spinal cord that receives input from fibers of the dorsal (posterior) root and sends information out through the fibers of the ventral (anterior) root. As discussed in this video, these connections represent the interactions of the CNS with peripheral structures for both sensory and motor functions. The cervical and lumbar spinal cords have enlargements as a result of larger populations of neurons. What are these enlargements responsible for?

Note:

Disorders of the...

Basal Nuclei

Parkinson's disease is a disorder of the basal nuclei, specifically of the substantia nigra, that demonstrates the effects of the direct and indirect pathways. Parkinson's disease is the result of neurons in the substantia nigra pars compacta dying. These neurons release dopamine into the striatum. Without that modulatory influence, the basal nuclei are stuck in the indirect pathway, without the direct pathway being activated. The direct pathway is responsible for increasing cortical movement commands. The increased activity of the indirect pathway results in the hypokinetic disorder of Parkinson's disease.

Parkinson's disease is neurodegenerative, meaning that neurons die that cannot be replaced, so there is no cure for the disorder. Treatments for Parkinson's disease are aimed at increasing dopamine levels in the striatum. Currently, the most common way of doing that is by providing the amino acid L-DOPA, which is a precursor to the neurotransmitter dopamine and can cross the blood-brain barrier. With levels of the precursor elevated, the remaining cells of the substantia nigra pars compacta can make more neurotransmitter and have a greater effect. Unfortunately, the patient will become less responsive to L-DOPA treatment as time progresses, and it can cause increased dopamine levels elsewhere in the brain, which are associated with psychosis or schizophrenia.

Note:

Visit this [site](#) for a thorough explanation of Parkinson's disease.

Note:

Compared with the nearest evolutionary relative, the chimpanzee, the human has a brain that is huge. At a point in the past, a common ancestor gave rise to the two species of humans and chimpanzees. That evolutionary history is long and is still an area of intense study. But something happened to increase the size of the human brain relative to the chimpanzee. Read [this article](#) in which the author explores the current understanding of why this happened.

According to one hypothesis about the expansion of brain size, what tissue might have been sacrificed so energy was available to grow our larger brain? Based on what you know about that tissue and nervous tissue, why would there be a trade-off between them in terms of energy use?

Chapter Review

The adult brain is separated into four major regions: the cerebrum, the diencephalon, the brain stem, and the cerebellum. The cerebrum is the largest portion and contains the cerebral cortex and subcortical nuclei. It is divided into two halves by the longitudinal fissure.

The cortex is separated into the frontal, parietal, temporal, and occipital lobes. The frontal lobe is responsible for motor functions, from planning movements through executing commands to be sent to the spinal cord and periphery. The most anterior portion of the frontal lobe is the prefrontal cortex, which is associated with aspects of personality through its influence on motor responses in decision-making.

The other lobes are responsible for sensory functions. The parietal lobe is where somatosensation is processed. The occipital lobe is where visual processing begins, although the other parts of the brain can contribute to visual function. The temporal lobe contains the cortical area for auditory processing, but also has regions crucial for memory formation.

Nuclei beneath the cerebral cortex, known as the subcortical nuclei, are responsible for augmenting cortical functions. The basal nuclei receive input from cortical areas and compare it with the general state of the individual through the activity of a dopamine-releasing nucleus. The output influences the activity of part of the thalamus that can then increase or decrease cortical activity that often results in changes to motor commands. The basal forebrain is responsible for modulating cortical activity in attention and memory. The limbic system includes deep cerebral nuclei that are responsible for emotion and memory.

The diencephalon includes the thalamus and the hypothalamus, along with some other structures. The thalamus is a relay between the cerebrum and the rest of the nervous system. The hypothalamus coordinates homeostatic functions through the autonomic and endocrine systems.

The brain stem is composed of the midbrain, pons, and medulla. It controls the head and neck region of the body through the cranial nerves. There are control centers in the brain stem that regulate the cardiovascular and respiratory systems.

The cerebellum is connected to the brain stem, primarily at the pons, where it receives a copy of the descending input from the cerebrum to the spinal cord. It can compare this with sensory feedback input through the medulla and send output through the midbrain that can correct motor commands for coordination.

Interactive Link Questions

Exercise:

Problem:

Watch this [video](#) to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the direct pathway is the shorter pathway through the system that results in increased activity in the cerebral cortex and increased motor activity. The direct pathway is described as resulting in “disinhibition” of the thalamus. What does disinhibition mean? What are the two neurons doing individually to cause this?

Solution:

Both cells are inhibitory. The first cell inhibits the second one. Therefore, the second cell can no longer inhibit its target. This is disinhibition of that target across two synapses.

Exercise:**Problem:**

Watch this [video](#) to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the indirect pathway is the longer pathway through the system that results in decreased activity in the cerebral cortex, and therefore less motor activity. The indirect pathway has an extra couple of connections in it, including disinhibition of the subthalamic nucleus. What is the end result on the thalamus, and therefore on movement initiated by the cerebral cortex?

Solution:

By disinhibiting the subthalamic nucleus, the indirect pathway increases excitation of the globus pallidus internal segment. That, in turn, inhibits the thalamus, which is the opposite effect of the direct pathway that disinhibits the thalamus.

Exercise:

Problem:

Watch this [video](#) to learn about the gray matter of the spinal cord that receives input from fibers of the dorsal (posterior) root and sends information out through the fibers of the ventral (anterior) root. As discussed in this video, these connections represent the interactions of the CNS with peripheral structures for both sensory and motor functions. The cervical and lumbar spinal cords have enlargements as a result of larger populations of neurons. What are these enlargements responsible for?

Solution:

There are more motor neurons in the anterior horns that are responsible for movement in the limbs. The cervical enlargement is for the arms, and the lumbar enlargement is for the legs.

Exercise:**Problem:**

Compared with the nearest evolutionary relative, the chimpanzee, the human has a brain that is huge. At a point in the past, a common ancestor gave rise to the two species of humans and chimpanzees. That evolutionary history is long and is still an area of intense study. But something happened to increase the size of the human brain relative to the chimpanzee. Read this [article](#) in which the author explores the current understanding of why this happened.

According to one hypothesis about the expansion of brain size, what tissue might have been sacrificed so energy was available to grow our larger brain? Based on what you know about that tissue and nervous tissue, why would there be a trade-off between them in terms of energy use?

Solution:

Energy is needed for the brain to develop and perform higher cognitive functions. That energy is not available for the muscle tissues to develop and function. The hypothesis suggests that humans have larger brains and less muscle mass, and chimpanzees have the smaller brains but more muscle mass.

Review Questions

Exercise:

Problem:

Which lobe of the cerebral cortex is responsible for generating motor commands?

- a. temporal
- b. parietal
- c. occipital
- d. frontal

Solution:

D

Exercise:

Problem: What region of the diencephalon coordinates homeostasis?

- a. thalamus
- b. epithalamus
- c. hypothalamus
- d. subthalamus

Solution:

C

Exercise:

Problem:

What level of the brain stem is the major input to the cerebellum?

- a. midbrain
- b. pons
- c. medulla
- d. spinal cord

Solution:

B

Exercise:

Problem:

What region of the spinal cord contains motor neurons that direct the movement of skeletal muscles?

- a. anterior horn
- b. posterior horn
- c. lateral horn
- d. alar plate

Solution:

A

Exercise:

Problem:

Brodmann's areas map different regions of the _____ to particular functions.

- a. cerebellum

- b. cerebral cortex
- c. basal forebrain
- d. corpus callosum

Solution:

B

Critical Thinking Questions

Exercise:

Problem:

Damage to specific regions of the cerebral cortex, such as through a stroke, can result in specific losses of function. What functions would likely be lost by a stroke in the temporal lobe?

Solution:

The temporal lobe has sensory functions associated with hearing and vision, as well as being important for memory. A stroke in the temporal lobe can result in specific sensory deficits in these systems (known as agnosias) or losses in memory.

Exercise:

Problem:

Why do the anatomical inputs to the cerebellum suggest that it can compare motor commands and sensory feedback?

Solution:

A copy of descending input from the cerebrum to the spinal cord, through the pons, and sensory feedback from the spinal cord and special senses like balance, through the medulla, both go to the

cerebellum. It can therefore send output through the midbrain that will correct spinal cord control of skeletal muscle movements.

Glossary

alar plate

developmental region of the spinal cord that gives rise to the posterior horn of the gray matter

amygdala

nucleus deep in the temporal lobe of the cerebrum that is related to memory and emotional behavior

anterior column

white matter between the anterior horns of the spinal cord composed of many different groups of axons of both ascending and descending tracts

anterior horn

gray matter of the spinal cord containing multipolar motor neurons, sometimes referred to as the ventral horn

anterior median fissure

deep midline feature of the anterior spinal cord, marking the separation between the right and left sides of the cord

ascending tract

central nervous system fibers carrying sensory information from the spinal cord or periphery to the brain

basal forebrain

nuclei of the cerebrum related to modulation of sensory stimuli and attention through broad projections to the cerebral cortex, loss of which is related to Alzheimer's disease

basal nuclei

nuclei of the cerebrum (with a few components in the upper brain stem and diencephalon) that are responsible for assessing cortical movement commands and comparing them with the general state of the individual through broad modulatory activity of dopamine neurons; largely related to motor functions, as evidenced through the symptoms of Parkinson's and Huntington's diseases

basal plate

developmental region of the spinal cord that gives rise to the lateral and anterior horns of gray matter

Broca's area

region of the frontal lobe associated with the motor commands necessary for speech production and located only in the cerebral hemisphere responsible for language production, which is the left side in approximately 95 percent of the population

Brodmann's areas

mapping of regions of the cerebral cortex based on microscopic anatomy that relates specific areas to functional differences, as described by Brodmann in the early 1900s

cauda equina

bundle of spinal nerve roots that descend from the lower spinal cord below the first lumbar vertebra and lie within the vertebral cavity; has the appearance of a horse's tail

caudate

nucleus deep in the cerebrum that is part of the basal nuclei; along with the putamen, it is part of the striatum

central sulcus

surface landmark of the cerebral cortex that marks the boundary between the frontal and parietal lobes

cerebral cortex

outer gray matter covering the forebrain, marked by wrinkles and folds known as gyri and sulci

cerebrum

region of the adult brain that develops from the telencephalon and is responsible for higher neurological functions such as memory, emotion, and consciousness

cerebellum

region of the adult brain connected primarily to the pons that developed from the metencephalon (along with the pons) and is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord

cerebral hemisphere

one half of the bilaterally symmetrical cerebrum

corpus callosum

large white matter structure that connects the right and left cerebral hemispheres

descending tract

central nervous system fibers carrying motor commands from the brain to the spinal cord or periphery

direct pathway

connections within the basal nuclei from the striatum to the globus pallidus internal segment and substantia nigra pars reticulata that disinhibit the thalamus to increase cortical control of movement

disinhibition

disynaptic connection in which the first synapse inhibits the second cell, which then stops inhibiting the final target

dorsal (posterior) nerve root

axons entering the posterior horn of the spinal cord

epithalamus

region of the diencephalon containing the pineal gland

frontal eye field

region of the frontal lobe associated with motor commands to orient the eyes toward an object of visual attention

frontal lobe

region of the cerebral cortex directly beneath the frontal bone of the cranium

globus pallidus

nuclei deep in the cerebrum that are part of the basal nuclei and can be divided into the internal and external segments

gyrus

ridge formed by convolutions on the surface of the cerebrum or cerebellum

hippocampus

gray matter deep in the temporal lobe that is very important for long-term memory formation

hypothalamus

major region of the diencephalon that is responsible for coordinating autonomic and endocrine control of homeostasis

indirect pathway

connections within the basal nuclei from the striatum through the globus pallidus external segment and subthalamic nucleus to the globus pallidus internal segment/substantia nigra pars compacta that result in inhibition of the thalamus to decrease cortical control of movement

inferior colliculus

half of the midbrain tectum that is part of the brain stem auditory pathway

inferior olive

nucleus in the medulla that is involved in processing information related to motor control

kinesthesia

general sensory perception of movement of the body

lateral column

white matter of the spinal cord between the posterior horn on one side and the axons from the anterior horn on the same side; composed of many different groups of axons, of both ascending and descending tracts, carrying motor commands to and from the brain

lateral horn

region of the spinal cord gray matter in the thoracic, upper lumbar, and sacral regions that is the central component of the sympathetic division of the autonomic nervous system

lateral sulcus

surface landmark of the cerebral cortex that marks the boundary between the temporal lobe and the frontal and parietal lobes

limbic cortex

collection of structures of the cerebral cortex that are involved in emotion, memory, and behavior and are part of the larger limbic system

limbic system

structures at the edge (limit) of the boundary between the forebrain and hindbrain that are most associated with emotional behavior and memory formation

longitudinal fissure

large separation along the midline between the two cerebral hemispheres

occipital lobe

region of the cerebral cortex directly beneath the occipital bone of the cranium

olfaction

special sense responsible for smell, which has a unique, direct connection to the cerebrum

parietal lobe

region of the cerebral cortex directly beneath the parietal bone of the cranium

parieto-occipital sulcus

groove in the cerebral cortex representing the border between the parietal and occipital cortices

postcentral gyrus

primary motor cortex located in the frontal lobe of the cerebral cortex

posterior columns

white matter of the spinal cord that lies between the posterior horns of the gray matter, sometimes referred to as the dorsal column; composed of axons of ascending tracts that carry sensory information up to the brain

posterior horn

gray matter region of the spinal cord in which sensory input arrives, sometimes referred to as the dorsal horn

posterior median sulcus

midline feature of the posterior spinal cord, marking the separation between right and left sides of the cord

posterolateral sulcus

feature of the posterior spinal cord marking the entry of posterior nerve roots and the separation between the posterior and lateral columns of the white matter

precentral gyrus

ridge just posterior to the central sulcus, in the parietal lobe, where somatosensory processing initially takes place in the cerebrum

prefrontal lobe

specific region of the frontal lobe anterior to the more specific motor function areas, which can be related to the early planning of movements and intentions to the point of being personality-type functions

premotor area

region of the frontal lobe responsible for planning movements that will be executed through the primary motor cortex

proprioception

general sensory perceptions providing information about location and movement of body parts; the “sense of the self”

putamen

nucleus deep in the cerebrum that is part of the basal nuclei; along with the caudate, it is part of the striatum

reticular formation

diffuse region of gray matter throughout the brain stem that regulates sleep, wakefulness, and states of consciousness

somatosensation

general senses related to the body, usually thought of as the senses of touch, which would include pain, temperature, and proprioception

striatum

the caudate and putamen collectively, as part of the basal nuclei, which receive input from the cerebral cortex

subcortical nucleus

all the nuclei beneath the cerebral cortex, including the basal nuclei and the basal forebrain

substantia nigra pars compacta

nuclei within the basal nuclei that release dopamine to modulate the function of the striatum; part of the motor pathway

substantia nigra pars reticulata

nuclei within the basal nuclei that serve as an output center of the nuclei; part of the motor pathway

subthalamus

nucleus within the basal nuclei that is part of the indirect pathway

sulcus

groove formed by convolutions in the surface of the cerebral cortex

superior colliculus

half of the midbrain tectum that is responsible for aligning visual, auditory, and somatosensory spatial perceptions

tectum

region of the midbrain, thought of as the roof of the cerebral aqueduct, which is subdivided into the inferior and superior colliculi

tegmentum

region of the midbrain, thought of as the floor of the cerebral aqueduct, which continues into the pons and medulla as the floor of the fourth ventricle

temporal lobe

region of the cerebral cortex directly beneath the temporal bone of the cranium

thalamus

major region of the diencephalon that is responsible for relaying information between the cerebrum and the hindbrain, spinal cord, and periphery

ventral (anterior) nerve root

axons emerging from the anterior or lateral horns of the spinal cord

The Peripheral Nervous System

By the end of this section, you will be able to:

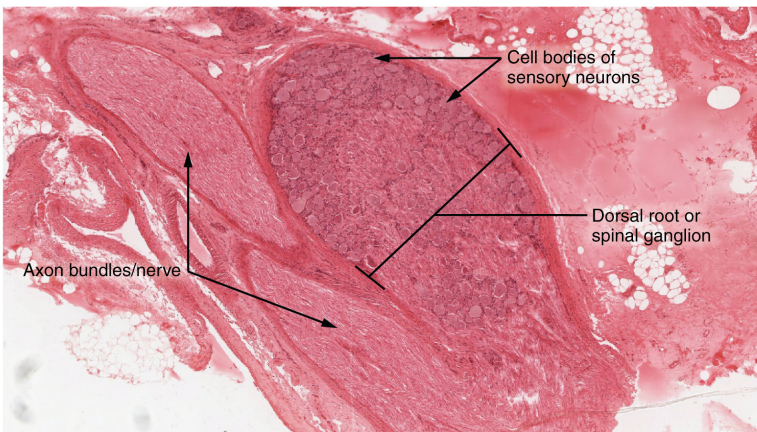
- Describe the structures found in the PNS
- Distinguish between somatic and autonomic structures, including the special peripheral structures of the enteric nervous system
- Name the twelve cranial nerves and explain the functions associated with each
- Describe the sensory and motor components of spinal nerves and the plexuses that they pass through

The PNS is not as contained as the CNS because it is defined as everything that is not the CNS. Some peripheral structures are incorporated into the other organs of the body. In describing the anatomy of the PNS, it is necessary to describe the common structures, the nerves and the ganglia, as they are found in various parts of the body. Many of the neural structures that are incorporated into other organs are features of the digestive system; these structures are known as the **enteric nervous system** and are a special subset of the PNS.

Ganglia

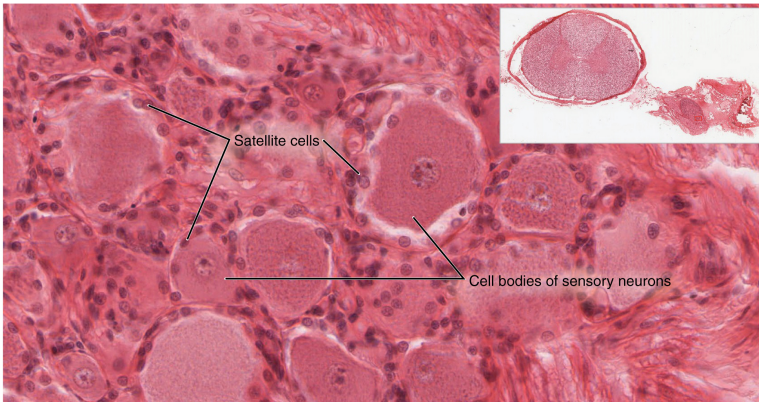
A ganglion is a group of neuron cell bodies in the periphery. Ganglia can be categorized, for the most part, as either sensory ganglia or autonomic ganglia, referring to their primary functions. The most common type of sensory ganglion is a **dorsal (posterior) root ganglion**. These ganglia are the cell bodies of neurons with axons that are sensory endings in the periphery, such as in the skin, and that extend into the CNS through the dorsal nerve root. The ganglion is an enlargement of the nerve root. Under microscopic inspection, it can be seen to include the cell bodies of the neurons, as well as bundles of fibers that are the posterior nerve root ([link](#)). The cells of the dorsal root ganglion are unipolar cells, classifying them by shape. Also, the small round nuclei of satellite cells can be seen surrounding—as if they were orbiting—the neuron cell bodies.

Dorsal Root Ganglion



The cell bodies of sensory neurons, which are unipolar neurons by shape, are seen in this photomicrograph. Also, the fibrous region is composed of the axons of these neurons that are passing through the ganglion to be part of the dorsal nerve root (tissue source: canine). LM $\times 40$. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Spinal Cord and Root Ganglion



The slide includes both a cross-section of the lumbar spinal cord and a section of the dorsal root ganglion (see also [link](#)) (tissue source: canine). LM $\times 1600$. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:



View the [University of Michigan WebScope](#) to explore the tissue sample in greater detail. If you zoom in on the dorsal root ganglion, you can see smaller satellite glial cells surrounding the large cell bodies of the sensory neurons. From what structure do satellite cells derive during embryologic development?

Another type of sensory ganglion is a **cranial nerve ganglion**. This is analogous to the dorsal root ganglion, except that it is associated with a **cranial nerve** instead of a **spinal nerve**. The roots of cranial nerves are within the cranium, whereas the ganglia are outside the skull. For example, the **trigeminal ganglion** is superficial to the temporal bone whereas its associated nerve is attached to the mid-pons region of the brain stem. The neurons of cranial nerve ganglia are also unipolar in shape with associated satellite cells.

The other major category of ganglia are those of the autonomic nervous system, which is divided into the sympathetic and parasympathetic nervous systems. The **sympathetic chain ganglia** constitute a row of ganglia along the vertebral column that receive central input from the lateral horn of the thoracic and upper lumbar spinal cord. Superior to the chain ganglia are three **paravertebral ganglia** in the cervical region. Three other autonomic ganglia that are related to the sympathetic chain are the **prevertebral ganglia**, which are located outside of the chain but have similar functions. They are referred to as prevertebral because they are anterior to the vertebral column. The neurons of these autonomic ganglia are multipolar in shape, with dendrites radiating out around the cell body where synapses from the spinal cord neurons are made. The neurons of the chain, paravertebral, and prevertebral ganglia then project to organs in the head and neck, thoracic, abdominal, and pelvic cavities to regulate the sympathetic aspect of homeostatic mechanisms.

Another group of autonomic ganglia are the **terminal ganglia** that receive input from cranial nerves or sacral spinal nerves and are responsible for regulating the parasympathetic aspect of homeostatic mechanisms. These two

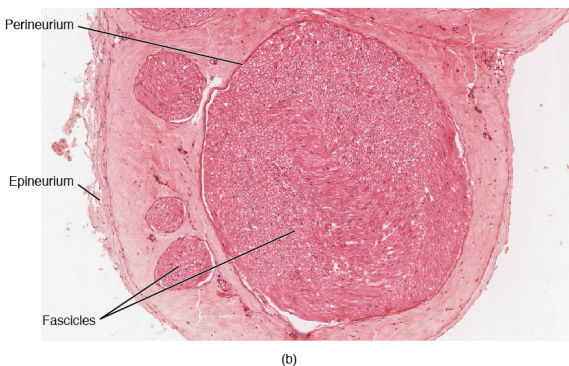
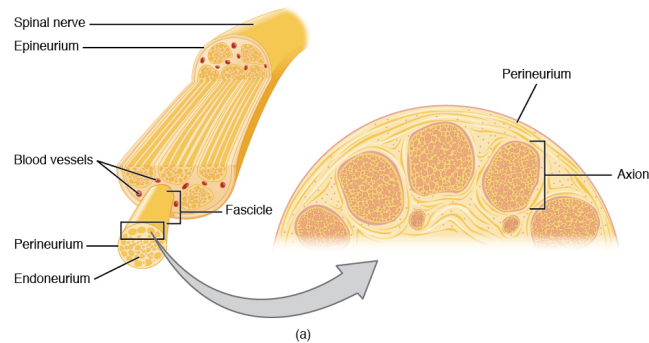
sets of ganglia, sympathetic and parasympathetic, often project to the same organs—one input from the chain ganglia and one input from a terminal ganglion—to regulate the overall function of an organ. For example, the heart receives two inputs such as these; one increases heart rate, and the other decreases it. The terminal ganglia that receive input from cranial nerves are found in the head and neck, as well as the thoracic and upper abdominal cavities, whereas the terminal ganglia that receive sacral input are in the lower abdominal and pelvic cavities.

Terminal ganglia below the head and neck are often incorporated into the wall of the target organ as a **plexus**. A plexus, in a general sense, is a network of fibers or vessels. This can apply to nervous tissue (as in this instance) or structures containing blood vessels (such as a choroid plexus). For example, the **enteric plexus** is the extensive network of axons and neurons in the wall of the small and large intestines. The enteric plexus is actually part of the enteric nervous system, along with the **gastric plexuses** and the **esophageal plexus**. Though the enteric nervous system receives input originating from central neurons of the autonomic nervous system, it does not require CNS input to function. In fact, it operates independently to regulate the digestive system.

Nerves

Bundles of axons in the PNS are referred to as nerves. These structures in the periphery are different than the central counterpart, called a tract. Nerves are composed of more than just nervous tissue. They have connective tissues invested in their structure, as well as blood vessels supplying the tissues with nourishment. The outer surface of a nerve is a surrounding layer of fibrous connective tissue called the **epineurium**. Within the nerve, axons are further bundled into **fascicles**, which are each surrounded by their own layer of fibrous connective tissue called **perineurium**. Finally, individual axons are surrounded by loose connective tissue called the **endoneurium** ([link](#)). These three layers are similar to the connective tissue sheaths for muscles. Nerves are associated with the region of the CNS to which they are connected, either as cranial nerves connected to the brain or spinal nerves connected to the spinal cord.

Nerve Structure



The structure of a nerve is organized by the layers of connective tissue on the outside, around each fascicle, and surrounding the individual nerve fibers (tissue source: simian). LM $\times 40$. (Micrograph provided by the Regents of University of Michigan Medical School)

Close-Up of Nerve Trunk



Zoom in on this slide of a nerve trunk to examine the endoneurium, perineurium, and epineurium in greater detail (tissue source: simian). LM $\times 1600$. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Note:



View the [University of Michigan WebScope](#) to explore the tissue sample in greater detail. With what structures in a skeletal muscle are the endoneurium, perineurium, and epineurium comparable?

Cranial Nerves

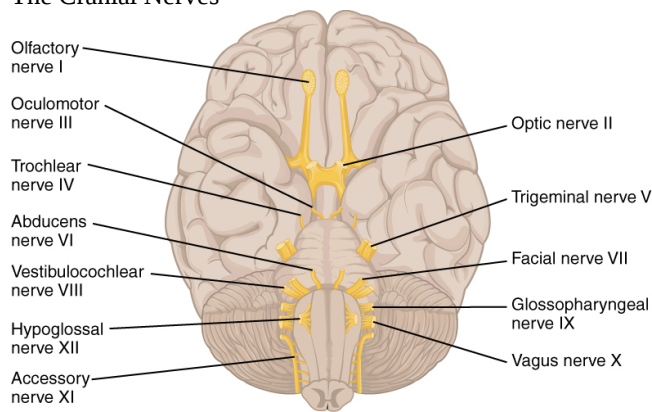
The nerves attached to the brain are the cranial nerves, which are primarily responsible for the sensory and motor functions of the head and neck (one of these nerves targets organs in the thoracic and abdominal cavities as part of the parasympathetic nervous system). There are twelve cranial nerves, which are designated CNI through CNXII for “Cranial Nerve,” using Roman numerals for 1 through 12. They can be classified as sensory nerves, motor nerves, or a combination of both, meaning that the axons in these nerves originate out of sensory ganglia external to the cranium or motor nuclei within the brain stem. Sensory axons enter the brain to synapse in a nucleus. Motor axons connect to skeletal muscles of the head or neck. Three of the nerves are solely composed of sensory fibers; five are strictly motor; and the remaining four are mixed nerves.

Learning the cranial nerves is a tradition in anatomy courses, and students have always used mnemonic devices to remember the nerve names. A traditional mnemonic is the rhyming couplet, “On Old Olympus’ Towering Tops/A Finn And German Viewed Some Hops,” in which the initial letter of each word corresponds to the initial letter in the name of each nerve. The names of the nerves have changed over the years to reflect current usage and more accurate naming. An exercise to help learn this sort of information is to generate a mnemonic using words that have personal significance. The names of the cranial nerves are listed in [\[link\]](#) along with a brief description of

their function, their source (sensory ganglion or motor nucleus), and their target (sensory nucleus or skeletal muscle). They are listed here with a brief explanation of each nerve ([link](#)).

The **olfactory nerve** and **optic nerve** are responsible for the sense of smell and vision, respectively. The **oculomotor nerve** is responsible for eye movements by controlling four of the **extraocular muscles**. It is also responsible for lifting the upper eyelid when the eyes point up, and for pupillary constriction. The **trochlear nerve** and the **abducens nerve** are both responsible for eye movement, but do so by controlling different extraocular muscles. The **trigeminal nerve** is responsible for cutaneous sensations of the face and controlling the muscles of mastication. The **facial nerve** is responsible for the muscles involved in facial expressions, as well as part of the sense of taste and the production of saliva. The **vestibulocochlear nerve** is responsible for the senses of hearing and balance. The **glossopharyngeal nerve** is responsible for controlling muscles in the oral cavity and upper throat, as well as part of the sense of taste and the production of saliva. The **vagus nerve** is responsible for contributing to homeostatic control of the organs of the thoracic and upper abdominal cavities. The **spinal accessory nerve** is responsible for controlling the muscles of the neck, along with cervical spinal nerves. The **hypoglossal nerve** is responsible for controlling the muscles of the lower throat and tongue.

The Cranial Nerves



The anatomical arrangement of the roots of the cranial nerves observed from an inferior view of the brain.

Three of the cranial nerves also contain autonomic fibers, and a fourth is almost purely a component of the autonomic system. The oculomotor, facial, and glossopharyngeal nerves contain fibers that contact autonomic ganglia. The oculomotor fibers initiate pupillary constriction, whereas the facial and glossopharyngeal fibers both initiate salivation. The vagus nerve primarily targets autonomic ganglia in the thoracic and upper abdominal cavities.

Note:



Visit this [site](#) to read about a man who wakes with a headache and a loss of vision. His regular doctor sent him to an ophthalmologist to address the vision loss. The ophthalmologist recognizes a greater problem and immediately sends him to the emergency room. Once there, the patient undergoes a large battery of tests, but a definite cause cannot be found. A specialist recognizes the problem as meningitis, but the question is what caused it originally.

How can that be cured? The loss of vision comes from swelling around the optic nerve, which probably presented as a bulge on the inside of the eye. Why is swelling related to meningitis going to push on the optic nerve?

Another important aspect of the cranial nerves that lends itself to a mnemonic is the functional role each nerve plays. The nerves fall into one of three basic groups. They are sensory, motor, or both (see [link](#)). The sentence, “Some Say Marry Money But My Brother Says Brains Beauty Matter More,” corresponds to the basic function of each nerve. The first, second, and eighth nerves are purely sensory: the olfactory (CNI), optic (CNII), and vestibulocochlear (CNVIII) nerves. The three eye-movement nerves are all motor: the oculomotor (CNIII), trochlear (CNIV), and abducens (CNVI). The spinal accessory (CNXI) and hypoglossal (CNXII) nerves are also strictly motor. The remainder of the nerves contain both sensory and motor fibers. They are the trigeminal (CNV), facial (CNVII), glossopharyngeal (CNIX), and vagus (CNX) nerves. The nerves that convey both are often related to each other. The trigeminal and facial nerves both concern the face; one concerns the sensations and the other concerns the muscle movements. The facial and glossopharyngeal nerves are both responsible for conveying gustatory, or taste, sensations as well as controlling salivary glands. The vagus nerve is involved in visceral responses to taste, namely the gag reflex. This is not an exhaustive list of what these combination nerves do, but there is a thread of relation between them.

| Cranial Nerves | | | | | |
|----------------|-----|------------|--------------------------|--|--|
| Mnemonic | # | Name | Function (S/M/B) | Central connection (nuclei) | |
| On | I | Olfactory | Smell (S) | Olfactory bulb | |
| Old | II | Optic | Vision (S) | Hypothalamus/thalamus/midbrain | |
| Olympus' | III | Oculomotor | Eye movements (M) | Oculomotor nucleus | |
| Towering | IV | Trochlear | Eye movements (M) | Trochlear nucleus | |
| Tops | V | Trigeminal | Sensory/motor – face (B) | Trigeminal nuclei in the midbrain, pons, and medulla | |
| A | VI | Abducens | Eye movements (M) | Abducens nucleus | |

| Cranial Nerves | | | | | |
|----------------|------|------------------------------|---|---|--|
| Mnemonic | # | Name | Function (S/M/B) | Central connection (nuclei) | |
| Finn | VII | Facial | Motor – face, Taste (B) | Facial nucleus, solitary nucleus, superior salivatory nucleus | |
| And | VIII | Auditory (Vestibulocochlear) | Hearing/balance (S) | Cochlear nucleus, Vestibular nucleus/cerebellum | |
| German | IX | Glossopharyngeal | Motor – throat Taste (B) | Solitary nucleus, inferior salivatory nucleus, nucleus ambiguus | |
| Viewed | X | Vagus | Motor/sensory – viscera (autonomic) (B) | Medulla | |
| Some | XI | Spinal Accessory | Motor – head and neck (M) | Spinal accessory nucleus | |
| Hops | XII | Hypoglossal | Motor – lower throat (M) | Hypoglossal nucleus | |

Spinal Nerves

The nerves connected to the spinal cord are the spinal nerves. The arrangement of these nerves is much more regular than that of the cranial nerves. All of the spinal nerves are combined sensory and motor axons that separate into two nerve roots. The sensory axons enter the spinal cord as the dorsal nerve root. The motor fibers, both somatic and autonomic, emerge as the ventral nerve root. The dorsal root ganglion for each nerve is an enlargement of the spinal nerve.

There are 31 spinal nerves, named for the level of the spinal cord at which each one emerges. There are eight pairs of cervical nerves designated C1 to C8, twelve thoracic nerves designated T1 to T12, five pairs of lumbar nerves

designated L1 to L5, five pairs of sacral nerves designated S1 to S5, and one pair of coccygeal nerves. The nerves are numbered from the superior to inferior positions, and each emerges from the vertebral column through the intervertebral foramen at its level. The first nerve, C1, emerges between the first cervical vertebra and the occipital bone. The second nerve, C2, emerges between the first and second cervical vertebrae. The same occurs for C3 to C7, but C8 emerges between the seventh cervical vertebra and the first thoracic vertebra. For the thoracic and lumbar nerves, each one emerges between the vertebra that has the same designation and the next vertebra in the column. The sacral nerves emerge from the sacral foramina along the length of that unique vertebra.

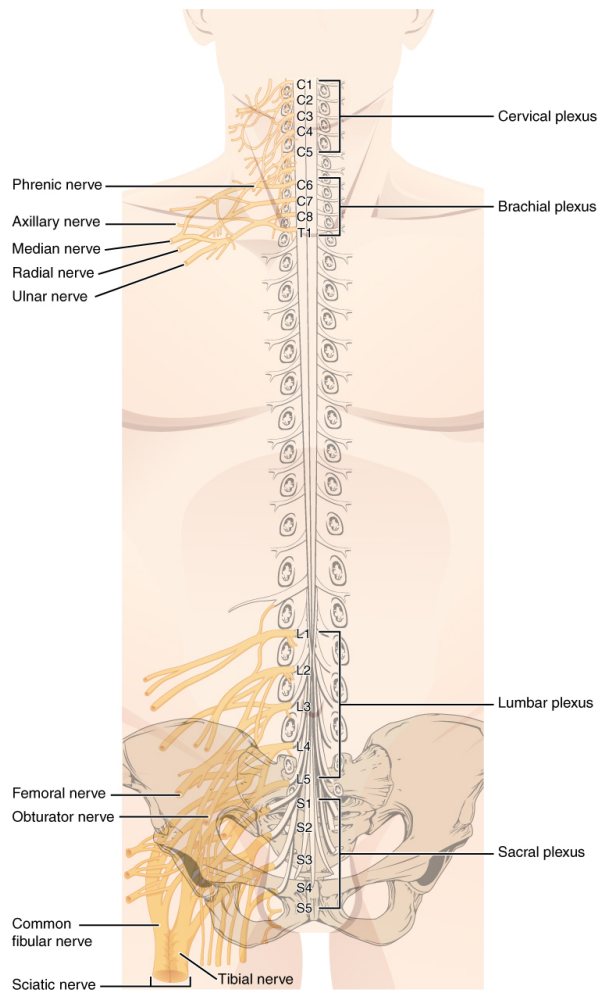
Spinal nerves extend outward from the vertebral column to enervate the periphery. The nerves in the periphery are not straight continuations of the spinal nerves, but rather the reorganization of the axons in those nerves to follow different courses. Axons from different spinal nerves will come together into a **systemic nerve**. This occurs at four places along the length of the vertebral column, each identified as a **nerve plexus**, whereas the other spinal nerves directly correspond to nerves at their respective levels. In this instance, the word plexus is used to describe networks of nerve fibers with no associated cell bodies.

Of the four nerve plexuses, two are found at the cervical level, one at the lumbar level, and one at the sacral level ([link](#)). The **cervical plexus** is composed of axons from spinal nerves C1 through C5 and branches into nerves in the posterior neck and head, as well as the **phrenic nerve**, which connects to the diaphragm at the base of the thoracic cavity. The other plexus from the cervical level is the **brachial plexus**. Spinal nerves C4 through T1 reorganize through this plexus to give rise to the nerves of the arms, as the name brachial suggests. A large nerve from this plexus is the **radial nerve** from which the **axillary nerve** branches to go to the armpit region. The radial nerve continues through the arm and is paralleled by the **ulnar nerve** and the **median nerve**. The **lumbar plexus** arises from all the lumbar spinal nerves and gives rise to nerves enervating the pelvic region and the anterior leg. The **femoral nerve** is one of the major nerves from this plexus, which gives rise to the **saphenous nerve** as a branch that extends through the anterior lower leg. The **sacral plexus** comes from the lower lumbar nerves L4 and L5 and the sacral nerves S1 to S4. The most significant systemic nerve to come from this plexus is the **sciatic nerve**, which is a combination of the **tibial nerve** and the **fibular nerve**. The sciatic nerve extends across the hip joint and is most commonly associated with the condition **sciatica**, which is the result of compression or irritation of the nerve or any of the spinal nerves giving rise to it.

These plexuses are described as arising from spinal nerves and giving rise to certain systemic nerves, but they contain fibers that serve sensory functions or fibers that serve motor functions. This means that some fibers extend from cutaneous or other peripheral sensory surfaces and send action potentials into the CNS. Those are axons of sensory neurons in the dorsal root ganglia that enter the spinal cord through the dorsal nerve root. Other fibers are the axons of motor neurons of the anterior horn of the spinal cord, which emerge in the ventral nerve root and send action potentials to cause skeletal muscles to contract in their target regions. For example, the radial nerve contains fibers of cutaneous sensation in the arm, as well as motor fibers that move muscles in the arm.

Spinal nerves of the thoracic region, T2 through T11, are not part of the plexuses but rather emerge and give rise to the **intercostal nerves** found between the ribs, which articulate with the vertebrae surrounding the spinal nerve.

Nerve Plexuses of the Body



There are four main nerve plexuses in the human body. The cervical plexus supplies nerves to the posterior head and neck, as well as to the diaphragm. The brachial plexus supplies nerves to the arm. The lumbar plexus supplies nerves to the anterior leg. The sacral plexus supplies nerves to the posterior leg.

Note:

Aging and the...

Nervous System

Anosmia is the loss of the sense of smell. It is often the result of the olfactory nerve being severed, usually because of blunt force trauma to the head. The sensory neurons of the olfactory epithelium have a limited lifespan of approximately one to four months, and new ones are made on a regular basis. The new neurons extend their axons into the CNS by growing along the existing fibers of the olfactory nerve. The ability of these neurons to be replaced is lost with age. Age-related anosmia is not the result of impact trauma to the head, but rather a slow loss of the sensory neurons with no new neurons born to replace them.

Smell is an important sense, especially for the enjoyment of food. There are only five tastes sensed by the tongue, and two of them are generally thought of as unpleasant tastes (sour and bitter). The rich sensory experience of

food is the result of odor molecules associated with the food, both as food is moved into the mouth, and therefore passes under the nose, and when it is chewed and molecules are released to move up the pharynx into the posterior nasal cavity. Anosmia results in a loss of the enjoyment of food.

As the replacement of olfactory neurons declines with age, anosmia can set in. Without the sense of smell, many sufferers complain of food tasting bland. Often, the only way to enjoy food is to add seasoning that can be sensed on the tongue, which usually means adding table salt. The problem with this solution, however, is that this increases sodium intake, which can lead to cardiovascular problems through water retention and the associated increase in blood pressure.

Chapter Review

The PNS is composed of the groups of neurons (ganglia) and bundles of axons (nerves) that are outside of the brain and spinal cord. Ganglia are of two types, sensory or autonomic. Sensory ganglia contain unipolar sensory neurons and are found on the dorsal root of all spinal nerves as well as associated with many of the cranial nerves. Autonomic ganglia are in the sympathetic chain, the associated paravertebral or prevertebral ganglia, or in terminal ganglia near or within the organs controlled by the autonomic nervous system.

Nerves are classified as cranial nerves or spinal nerves on the basis of their connection to the brain or spinal cord, respectively. The twelve cranial nerves can be strictly sensory in function, strictly motor in function, or a combination of the two functions. Sensory fibers are axons of sensory ganglia that carry sensory information into the brain and target sensory nuclei. Motor fibers are axons of motor neurons in motor nuclei of the brain stem and target skeletal muscles of the head and neck. Spinal nerves are all mixed nerves with both sensory and motor fibers. Spinal nerves emerge from the spinal cord and reorganize through plexuses, which then give rise to systemic nerves. Thoracic spinal nerves are not part of any plexus, but give rise to the intercostal nerves directly.

Interactive Link Questions

Exercise:

Problem:

[\[link\]](#) If you zoom in on the DRG, you can see smaller satellite glial cells surrounding the large cell bodies of the sensory neurons. From what structure do satellite cells derive during embryologic development?

Solution:

[\[link\]](#) They derive from the neural crest.

Exercise:

Problem:

[\[link\]](#) To what structures in a skeletal muscle are the endoneurium, perineurium, and epineurium comparable?

Solution:

[\[link\]](#) The endoneurium surrounding individual nerve fibers is comparable to the endomysium surrounding myofibrils, the perineurium bundling axons into fascicles is comparable to the perimysium bundling muscle fibers into fascicles, and the epineurium surrounding the whole nerve is comparable to the epimysium surrounding the muscle.

Exercise:

Problem:

Visit this [site](#) to read about a man who wakes with a headache and a loss of vision. His regular doctor sent him to an ophthalmologist to address the vision loss. The ophthalmologist recognizes a greater problem and immediately sends him to the emergency room. Once there, the patient undergoes a large battery of tests, but a definite cause cannot be found. A specialist recognizes the problem as meningitis, but the question is what caused it originally. How can that be cured? The loss of vision comes from swelling around the optic nerve, which probably presented as a bulge on the inside of the eye. Why is swelling related to meningitis going to push on the optic nerve?

Solution:

The optic nerve enters the CNS in its projection from the eyes in the periphery, which means that it crosses through the meninges. Meningitis will include swelling of those protective layers of the CNS, resulting in pressure on the optic nerve, which can compromise vision.

Review Questions**Exercise:**

Problem: What type of ganglion contains neurons that control homeostatic mechanisms of the body?

- a. sensory ganglion
 - b. dorsal root ganglion
 - c. autonomic ganglion
 - d. cranial nerve ganglion
-

Solution:

C

Exercise:

Problem: Which ganglion is responsible for cutaneous sensations of the face?

- a. otic ganglion
 - b. vestibular ganglion
 - c. geniculate ganglion
 - d. trigeminal ganglion
-

Solution:

D

Exercise:

Problem: What is the name for a bundle of axons within a nerve?

- a. fascicle
- b. tract
- c. nerve root
- d. epineurium

Solution:

A

Exercise:

Problem: Which cranial nerve does not control functions in the head and neck?

- a. olfactory
- b. trochlear
- c. glossopharyngeal
- d. vagus

Solution:

D

Exercise:

Problem: Which of these structures is not under direct control of the peripheral nervous system?

- a. trigeminal ganglion
- b. gastric plexus
- c. sympathetic chain ganglia
- d. cervical plexus

Solution:

B

Critical Thinking Questions**Exercise:**

Problem: Why are ganglia and nerves not surrounded by protective structures like the meninges of the CNS?

Solution:

The peripheral nervous tissues are out in the body, sometimes part of other organ systems. There is not a privileged blood supply like there is to the brain and spinal cord, so peripheral nervous tissues do not need the same sort of protections.

Exercise:**Problem:**

Testing for neurological function involves a series of tests of functions associated with the cranial nerves. What functions, and therefore which nerves, are being tested by asking a patient to follow the tip of a pen with their eyes?

Solution:

The contraction of extraocular muscles is being tested, which is the function of the oculomotor, trochlear, and abducens nerves.

Glossary

abducens nerve

sixth cranial nerve; responsible for contraction of one of the extraocular muscles

axillary nerve

systemic nerve of the arm that arises from the brachial plexus

brachial plexus

nerve plexus associated with the lower cervical spinal nerves and first thoracic spinal nerve

cervical plexus

nerve plexus associated with the upper cervical spinal nerves

cranial nerve

one of twelve nerves connected to the brain that are responsible for sensory or motor functions of the head and neck

cranial nerve ganglion

sensory ganglion of cranial nerves

dorsal (posterior) root ganglion

sensory ganglion attached to the posterior nerve root of a spinal nerve

endoneurium

innermost layer of connective tissue that surrounds individual axons within a nerve

enteric nervous system

peripheral structures, namely ganglia and nerves, that are incorporated into the digestive system organs

enteric plexus

neuronal plexus in the wall of the intestines, which is part of the enteric nervous system

epineurium

outermost layer of connective tissue that surrounds an entire nerve

esophageal plexus

neuronal plexus in the wall of the esophagus that is part of the enteric nervous system

extraocular muscles

six skeletal muscles that control eye movement within the orbit

facial nerve

seventh cranial nerve; responsible for contraction of the facial muscles and for part of the sense of taste, as well as causing saliva production

fascicle

small bundles of nerve or muscle fibers enclosed by connective tissue

femoral nerve

systemic nerve of the anterior leg that arises from the lumbar plexus

fibular nerve

systemic nerve of the posterior leg that begins as part of the sciatic nerve

gastric plexuses

neuronal networks in the wall of the stomach that are part of the enteric nervous system

glossopharyngeal nerve

ninth cranial nerve; responsible for contraction of muscles in the tongue and throat and for part of the sense of taste, as well as causing saliva production

hypoglossal nerve

twelfth cranial nerve; responsible for contraction of muscles of the tongue

intercostal nerve

systemic nerve in the thoracic cavity that is found between two ribs

lumbar plexus

nerve plexus associated with the lumbar spinal nerves

median nerve

systemic nerve of the arm, located between the ulnar and radial nerves

nerve plexus

network of nerves without neuronal cell bodies included

oculomotor nerve

third cranial nerve; responsible for contraction of four of the extraocular muscles, the muscle in the upper eyelid, and pupillary constriction

olfactory nerve

first cranial nerve; responsible for the sense of smell

optic nerve

second cranial nerve; responsible for visual sensation

paravertebral ganglia

autonomic ganglia superior to the sympathetic chain ganglia

perineurium

layer of connective tissue surrounding fascicles within a nerve

phrenic nerve

systemic nerve from the cervical plexus that innervates the diaphragm

plexus

network of nerves or nervous tissue

prevertebral ganglia

autonomic ganglia that are anterior to the vertebral column and functionally related to the sympathetic chain ganglia

radial nerve

systemic nerve of the arm, the distal component of which is located near the radial bone

sacral plexus

nerve plexus associated with the lower lumbar and sacral spinal nerves

saphenous nerve

systemic nerve of the lower anterior leg that is a branch from the femoral nerve

sciatic nerve

systemic nerve from the sacral plexus that is a combination of the tibial and fibular nerves and extends across the hip joint and gluteal region into the upper posterior leg

sciatica

painful condition resulting from inflammation or compression of the sciatic nerve or any of the spinal nerves that contribute to it

spinal accessory nerve

eleventh cranial nerve; responsible for contraction of neck muscles

spinal nerve

one of 31 nerves connected to the spinal cord

sympathetic chain ganglia

autonomic ganglia in a chain along the anterolateral aspect of the vertebral column that are responsible for contributing to homeostatic mechanisms of the autonomic nervous system

systemic nerve

nerve in the periphery distal to a nerve plexus or spinal nerve

terminal ganglion

autonomic ganglia that are near or within the walls of organs that are responsible for contributing to homeostatic mechanisms of the autonomic nervous system

tibial nerve

systemic nerve of the posterior leg that begins as part of the sciatic nerve

trigeminal ganglion

sensory ganglion that contributes sensory fibers to the trigeminal nerve

trigeminal nerve

fifth cranial nerve; responsible for cutaneous sensation of the face and contraction of the muscles of mastication

trochlear nerve

fourth cranial nerve; responsible for contraction of one of the extraocular muscles

ulnar nerve

systemic nerve of the arm located close to the ulna, a bone of the forearm

vagus nerve

tenth cranial nerve; responsible for the autonomic control of organs in the thoracic and upper abdominal cavities

vestibulocochlear nerve

eighth cranial nerve; responsible for the sensations of hearing and balance

Introduction

class="introduction"

Fight or Flight?

Though the threats that modern humans face are not large predators, the autonomic nervous system is adapted to this type of stimulus.

The modern world presents stimuli that trigger the same response.

(credit:
Vernon
Swanepoel
)



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Describe the components of the autonomic nervous system
- Differentiate between the structures of the sympathetic and parasympathetic divisions in the autonomic nervous system
- Name the components of a visceral reflex specific to the autonomic division to which it belongs
- Predict the response of a target effector to autonomic input on the basis of the released signaling molecule
- Describe how the central nervous system coordinates and contributes to autonomic functions

The autonomic nervous system is often associated with the “fight-or-flight response,” which refers to the preparation of the body to either run away

from a threat or to stand and fight in the face of that threat. To suggest what this means, consider the (very unlikely) situation of seeing a lioness hunting out on the savannah. Though this is not a common threat that humans deal with in the modern world, it represents the type of environment in which the human species thrived and adapted. The spread of humans around the world to the present state of the modern age occurred much more quickly than any species would adapt to environmental pressures such as predators. However, the reactions modern humans have in the modern world are based on these prehistoric situations. If your boss is walking down the hallway on Friday afternoon looking for “volunteers” to come in on the weekend, your response is the same as the prehistoric human seeing the lioness running across the savannah: fight or flight.

Most likely, your response to your boss—not to mention the lioness—would be flight. Run away! The autonomic system is responsible for the physiological response to make that possible, and hopefully successful. Adrenaline starts to flood your circulatory system. Your heart rate increases. Sweat glands become active. The bronchi of the lungs dilate to allow more air exchange. Pupils dilate to increase visual information. Blood pressure increases in general, and blood vessels dilate in skeletal muscles. Time to run. Similar physiological responses would occur in preparation for fighting off the threat.

This response should sound a bit familiar. The autonomic nervous system is tied into emotional responses as well, and the fight-or-flight response probably sounds like a panic attack. In the modern world, these sorts of reactions are associated with anxiety as much as with response to a threat. It is engrained in the nervous system to respond like this. In fact, the adaptations of the autonomic nervous system probably predate the human species and are likely to be common to all mammals, and perhaps shared by many animals. That lioness might herself be threatened in some other situation.

However, the autonomic nervous system is not just about responding to threats. Besides the fight-or-flight response, there are the responses referred to as “rest and digest.” If that lioness is successful in her hunting, then she is going to rest from the exertion. Her heart rate will slow. Breathing will

return to normal. The digestive system has a big job to do. Much of the function of the autonomic system is based on the connections within an autonomic, or visceral, reflex.

Divisions of the Autonomic Nervous System

By the end of this section, you will be able to:

- Name the components that generate the sympathetic and parasympathetic responses of the autonomic nervous system
- Explain the differences in output connections within the two divisions of the autonomic nervous system
- Describe the signaling molecules and receptor proteins involved in communication within the two divisions of the autonomic nervous system

The nervous system can be divided into two functional parts: the somatic nervous system and the autonomic nervous system. The major differences between the two systems are evident in the responses that each produces. The somatic nervous system causes contraction of skeletal muscles. The autonomic nervous system controls cardiac and smooth muscle, as well as glandular tissue. The somatic nervous system is associated with voluntary responses (though many can happen without conscious awareness, like breathing), and the autonomic nervous system is associated with involuntary responses, such as those related to homeostasis.

The autonomic nervous system regulates many of the internal organs through a balance of two aspects, or divisions. In addition to the endocrine system, the autonomic nervous system is instrumental in homeostatic mechanisms in the body. The two divisions of the autonomic nervous system are the **sympathetic division** and the **parasympathetic division**. The sympathetic system is associated with the **fight-or-flight response**, and parasympathetic activity is referred to by the epithet of **rest and digest**. Homeostasis is the balance between the two systems. At each target effector, dual innervation determines activity. For example, the heart receives connections from both the sympathetic and parasympathetic divisions. One causes heart rate to increase, whereas the other causes heart rate to decrease.

Note:



Watch this [video](#) to learn more about adrenaline and the fight-or-flight response. When someone is said to have a rush of adrenaline, the image of bungee jumpers or skydivers usually comes to mind. But adrenaline, also known as epinephrine, is an important chemical in coordinating the body's fight-or-flight response. In this video, you look inside the physiology of the fight-or-flight response, as envisioned for a firefighter. His body's reaction is the result of the sympathetic division of the autonomic nervous system causing system-wide changes as it prepares for extreme responses. What two changes does adrenaline bring about to help the skeletal muscle response?

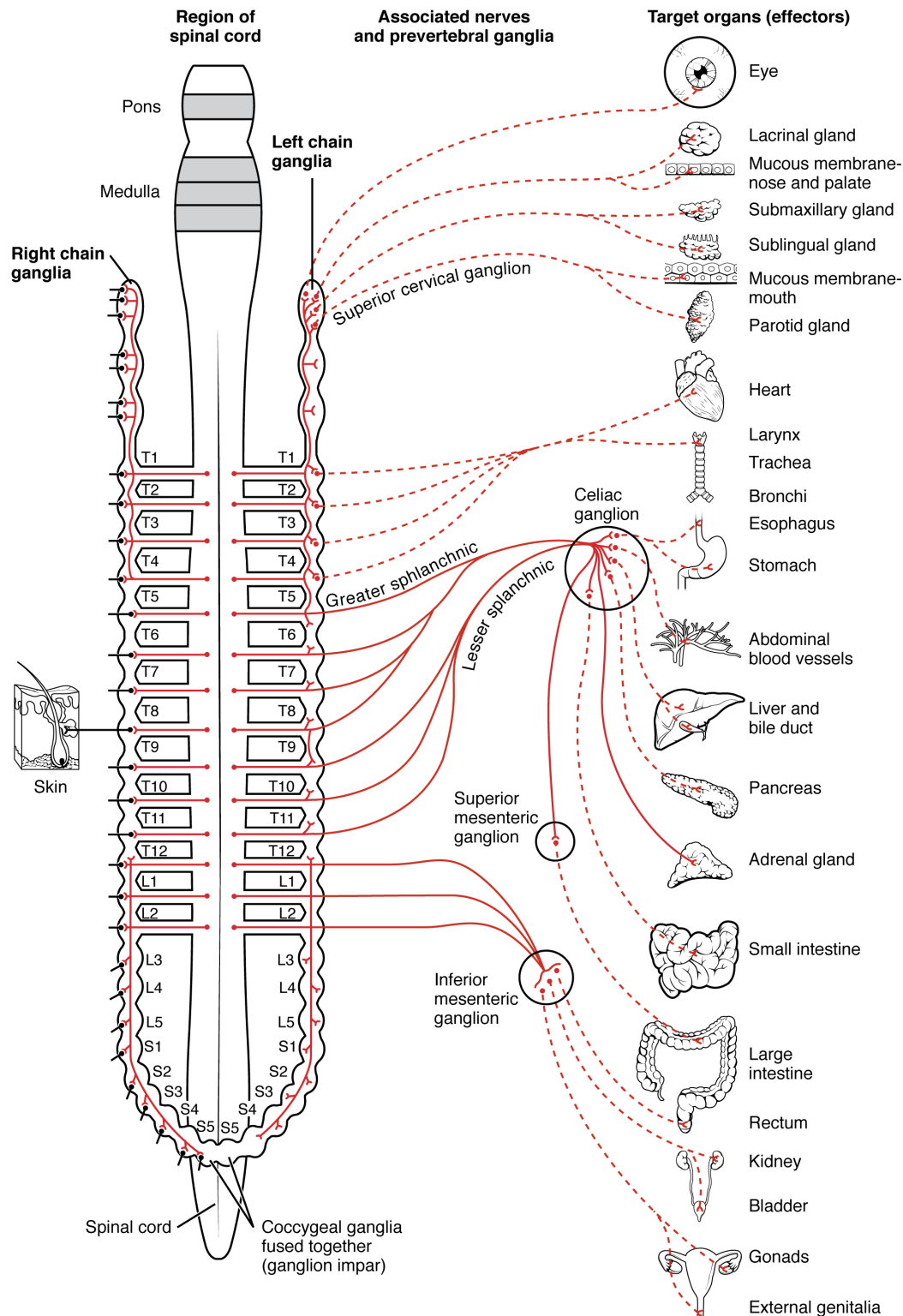
Sympathetic Division of the Autonomic Nervous System

To respond to a threat—to fight or to run away—the sympathetic system causes divergent effects as many different effector organs are activated together for a common purpose. More oxygen needs to be inhaled and delivered to skeletal muscle. The respiratory, cardiovascular, and musculoskeletal systems are all activated together. Additionally, sweating keeps the excess heat that comes from muscle contraction from causing the body to overheat. The digestive system shuts down so that blood is not absorbing nutrients when it should be delivering oxygen to skeletal muscles. To coordinate all these responses, the connections in the sympathetic system diverge from a limited region of the central nervous system (CNS) to a wide array of ganglia that project to the many effector organs simultaneously. The complex set of structures that compose the output of the sympathetic system make it possible for these disparate effectors to come together in a coordinated, systemic change.

The sympathetic division of the autonomic nervous system influences the various organ systems of the body through connections emerging from the thoracic and upper lumbar spinal cord. It is referred to as the **thoracolumbar system** to reflect this anatomical basis. A **central neuron** in the lateral horn of any of these spinal regions projects to ganglia adjacent to the vertebral column through the ventral spinal roots. The majority of ganglia of the sympathetic system belong to a network of **sympathetic chain ganglia** that runs alongside the vertebral column. The ganglia appear as a series of clusters of neurons linked by axonal bridges. There are typically 23 ganglia in the chain on either side of the spinal column. Three correspond to the cervical region, 12 are in the thoracic region, four are in the lumbar region, and four correspond to the sacral region. The cervical and sacral levels are not connected to the spinal cord directly through the spinal roots, but through ascending or descending connections through the bridges within the chain.

A diagram that shows the connections of the sympathetic system is somewhat like a circuit diagram that shows the electrical connections between different receptacles and devices. In [\[link\]](#), the “circuits” of the sympathetic system are intentionally simplified.

Connections of Sympathetic Division of the Autonomic Nervous System



Neurons from the lateral horn of the spinal cord (preganglionic nerve fibers - solid lines) project to the chain ganglia on either side of the vertebral column or to

collateral (prevertebral) ganglia that are anterior to the vertebral column in the abdominal cavity. Axons from these ganglionic neurons (postganglionic nerve fibers - dotted lines) then project to target effectors throughout the body.

To continue with the analogy of the circuit diagram, there are three different types of “junctions” that operate within the sympathetic system ([\[link\]](#)). The first type is most direct: the sympathetic nerve projects to the chain ganglion at the same level as the **target effector** (the organ, tissue, or gland to be innervated). An example of this type is spinal nerve T1 that synapses with the T1 chain ganglion to innervate the trachea. The fibers of this branch are called **white rami communicantes** (singular = ramus communicans); they are myelinated and therefore referred to as white (see [\[link\]a](#)). The axon from the central neuron (the preganglionic fiber shown as a solid line) synapses with the **ganglionic neuron** (with the postganglionic fiber shown as a dashed line). This neuron then projects to a target effector—in this case, the trachea—via **gray rami communicantes**, which are unmyelinated axons.

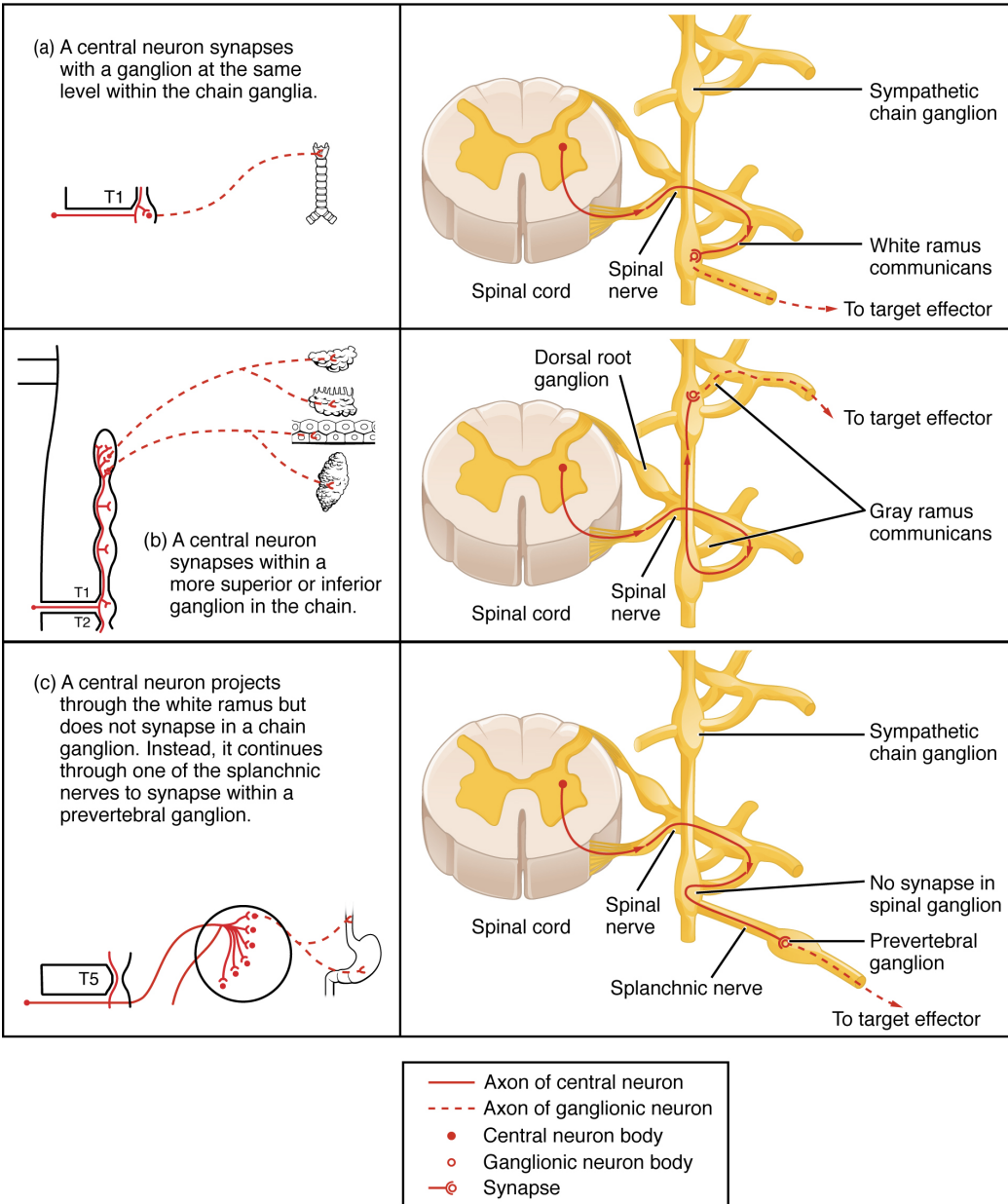
In some cases, the target effectors are located superior or inferior to the spinal segment at which the preganglionic fiber emerges. With respect to the “wiring” involved, the synapse with the ganglionic neuron occurs at chain ganglia superior or inferior to the location of the central neuron. An example of this is spinal nerve T1 that innervates the eye. The spinal nerve tracks up through the chain until it reaches the **superior cervical ganglion**, where it synapses with the postganglionic neuron (see [\[link\]b](#)). The cervical ganglia are referred to as **paravertebral ganglia**, given their location adjacent to prevertebral ganglia in the sympathetic chain.

Not all axons from the central neurons terminate in the chain ganglia. Additional branches from the ventral nerve root continue through the chain and on to one of the collateral ganglia as the **greater splanchnic nerve** or **lesser splanchnic nerve**. For example, the greater splanchnic nerve at the level of T5 synapses with a collateral ganglion outside the chain before

making the connection to the postganglionic nerves that innervate the stomach (see [\[link\]](#)c).

Collateral ganglia, also called **prevertebral ganglia**, are situated anterior to the vertebral column and receive inputs from splanchnic nerves as well as central sympathetic neurons. They are associated with controlling organs in the abdominal cavity, and are also considered part of the enteric nervous system. The three collateral ganglia are the **celiac ganglion**, the **superior mesenteric ganglion**, and the **inferior mesenteric ganglion** (see [\[link\]](#)). The word celiac is derived from the Latin word “coelom,” which refers to a body cavity (in this case, the abdominal cavity), and the word mesenteric refers to the digestive system.

Sympathetic Connections and Chain Ganglia



The axon from a central sympathetic neuron in the spinal cord can project to the periphery in a number of different ways. (a) The fiber can project out to the ganglion at the same level and synapse on a ganglionic neuron. (b) A branch can project to more superior or inferior ganglion in the chain. (c) A branch can project through the white ramus communicans, but not terminate on a ganglionic neuron in the chain. Instead, it projects through one of the splanchnic

nerves to a collateral ganglion or the adrenal medulla (not pictured).

An axon from the central neuron that projects to a sympathetic ganglion is referred to as a **preganglionic fiber** or neuron, and represents the output from the CNS to the ganglion. Because the sympathetic ganglia are adjacent to the vertebral column, preganglionic sympathetic fibers are relatively short, and they are myelinated. A **postganglionic fiber**—the axon from a ganglionic neuron that projects to the target effector—represents the output of a ganglion that directly influences the organ. Compared with the preganglionic fibers, postganglionic sympathetic fibers are long because of the relatively greater distance from the ganglion to the target effector. These fibers are unmyelinated. (Note that the term “postganglionic neuron” may be used to describe the projection from a ganglion to the target. The problem with that usage is that the cell body is in the ganglion, and only the fiber is postganglionic. Typically, the term neuron applies to the entire cell.)

One type of preganglionic sympathetic fiber does not terminate in a ganglion. These are the axons from central sympathetic neurons that project to the **adrenal medulla**, the interior portion of the adrenal gland. These axons are still referred to as preganglionic fibers, but the target is not a ganglion. The adrenal medulla releases signaling molecules into the bloodstream, rather than using axons to communicate with target structures. The cells in the adrenal medulla that are contacted by the preganglionic fibers are called **chromaffin cells**. These cells are neurosecretory cells that develop from the neural crest along with the sympathetic ganglia, reinforcing the idea that the gland is, functionally, a sympathetic ganglion.

The projections of the sympathetic division of the autonomic nervous system diverge widely, resulting in a broad influence of the system throughout the body. As a response to a threat, the sympathetic system would increase heart rate and breathing rate and cause blood flow to the skeletal muscle to increase and blood flow to the digestive system to decrease. Sweat gland secretion should also increase as part of an integrated response. All of those physiological changes are going to be required to occur together to run away from the hunting lioness, or the modern equivalent. This divergence is seen in the branching patterns of

preganglionic sympathetic neurons—a single preganglionic sympathetic neuron may have 10–20 targets. An axon that leaves a central neuron of the lateral horn in the thoracolumbar spinal cord will pass through the white ramus communicans and enter the sympathetic chain, where it will branch toward a variety of targets. At the level of the spinal cord at which the preganglionic sympathetic fiber exits the spinal cord, a branch will synapse on a neuron in the adjacent chain ganglion. Some branches will extend up or down to a different level of the chain ganglia. Other branches will pass through the chain ganglia and project through one of the splanchnic nerves to a collateral ganglion. Finally, some branches may project through the splanchnic nerves to the adrenal medulla. All of these branches mean that one preganglionic neuron can influence different regions of the sympathetic system very broadly, by acting on widely distributed organs.

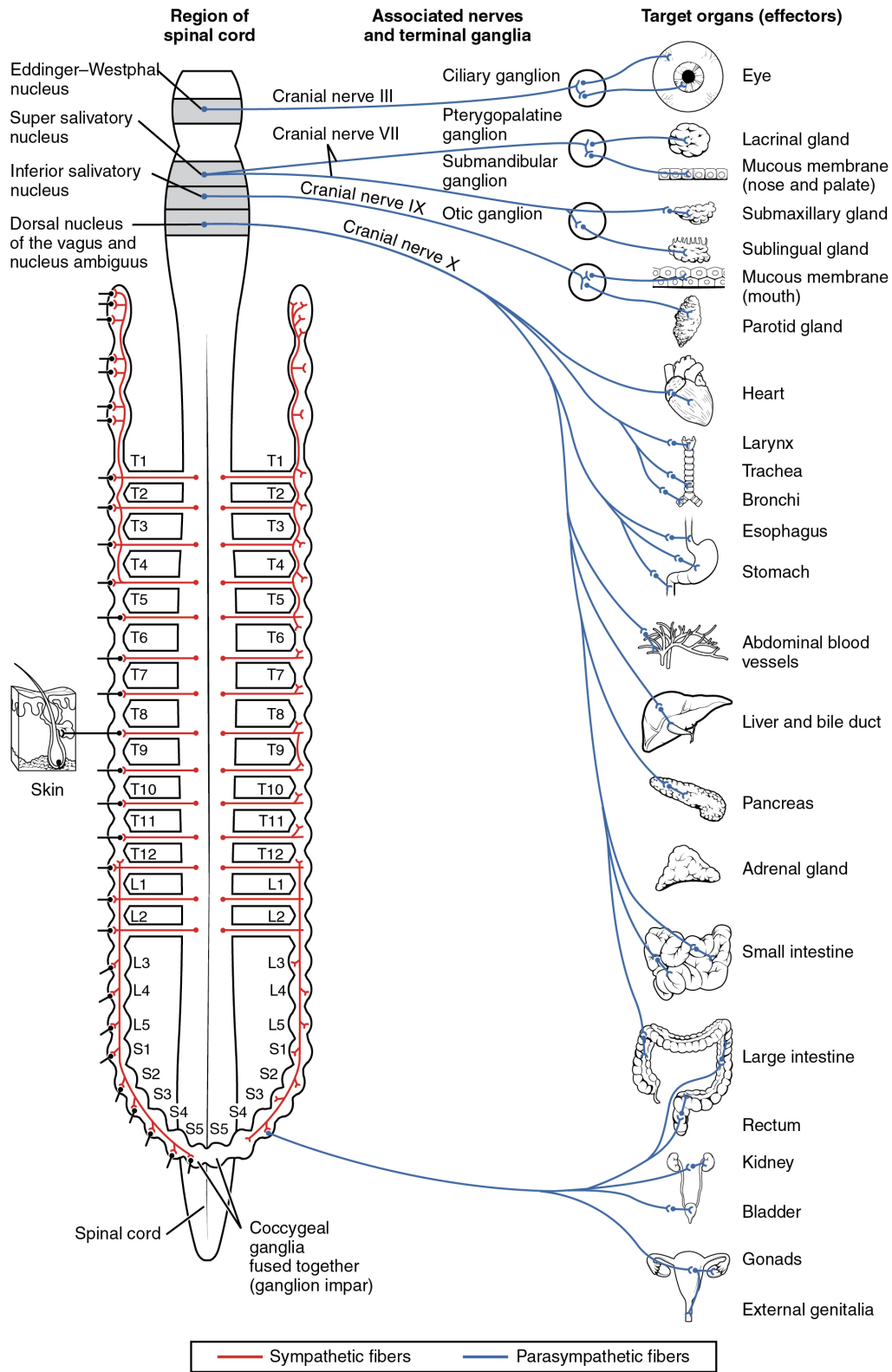
Parasympathetic Division of the Autonomic Nervous System

The parasympathetic division of the autonomic nervous system is named because its central neurons are located on either side of the thoracolumbar region of the spinal cord (para- = “beside” or “near”). The parasympathetic system can also be referred to as the **craniosacral system** (or outflow) because the preganglionic neurons are located in nuclei of the brain stem and the lateral horn of the sacral spinal cord.

The connections, or “circuits,” of the parasympathetic division are similar to the general layout of the sympathetic division with a few specific differences ([\[link\]](#)). The preganglionic fibers from the cranial region travel in cranial nerves, whereas preganglionic fibers from the sacral region travel in spinal nerves. The targets of these fibers are **terminal ganglia**, which are located near—or even within—the target effector. These ganglia are often referred to as **intramural ganglia** when they are found within the walls of the target organ. The postganglionic fiber projects from the terminal ganglia a short distance to the target effector, or to the specific target tissue within the organ. Comparing the relative lengths of axons in the parasympathetic system, the preganglionic fibers are long and the postganglionic fibers are short because the ganglia are close to—and sometimes within—the target effectors.

The cranial component of the parasympathetic system is based in particular nuclei of the brain stem. In the midbrain, the **Edinger–Westphal nucleus** is part of the oculomotor complex, and axons from those neurons travel with the fibers in the oculomotor nerve (cranial nerve III) that innervate the extraocular muscles. The preganglionic parasympathetic fibers within cranial nerve III terminate in the **ciliary ganglion**, which is located in the posterior orbit. The postganglionic parasympathetic fibers then project to the smooth muscle of the iris to control pupillary size. In the upper medulla, the salivatory nuclei contain neurons with axons that project through the facial and glossopharyngeal nerves to ganglia that control salivary glands. Tear production is influenced by parasympathetic fibers in the facial nerve, which activate a ganglion, and ultimately the lacrimal (tear) gland. Neurons in the **dorsal nucleus of the vagus nerve** and the **nucleus ambiguus** project through the vagus nerve (cranial nerve X) to the terminal ganglia of the thoracic and abdominal cavities. Parasympathetic preganglionic fibers primarily influence the heart, bronchi, and esophagus in the thoracic cavity and the stomach, liver, pancreas, gall bladder, and small intestine of the abdominal cavity. The postganglionic fibers from the ganglia activated by the vagus nerve are often incorporated into the structure of the organ, such as the **mesenteric plexus** of the digestive tract organs and the intramural ganglia.

Connections of Parasympathetic Division of the Autonomic Nervous System



Neurons from brain-stem nuclei, or from the lateral horn of

the sacral spinal cord, project to terminal ganglia near or within the various organs of the body. Axons from these ganglionic neurons then project the short distance to those target effectors.

Chemical Signaling in the Autonomic Nervous System

Where an autonomic neuron connects with a target, there is a synapse. The electrical signal of the action potential causes the release of a signaling molecule, which will bind to receptor proteins on the target cell. Synapses of the autonomic system are classified as either **cholinergic**, meaning that **acetylcholine (ACh)** is released, or **adrenergic**, meaning that **norepinephrine** is released. The terms cholinergic and adrenergic refer not only to the signaling molecule that is released but also to the class of receptors that each binds.

The cholinergic system includes two classes of receptor: the **nicotinic receptor** and the **muscarinic receptor**. Both receptor types bind to ACh and cause changes in the target cell. The nicotinic receptor is a **ligand-gated cation channel** and the muscarinic receptor is a **G protein-coupled receptor**. The receptors are named for, and differentiated by, other molecules that bind to them. Whereas nicotine will bind to the nicotinic receptor, and muscarine will bind to the muscarinic receptor, there is no cross-reactivity between the receptors. The situation is similar to locks and keys. Imagine two locks—one for a classroom and the other for an office—that are opened by two separate keys. The classroom key will not open the office door and the office key will not open the classroom door. This is similar to the specificity of nicotine and muscarine for their receptors. However, a master key can open multiple locks, such as a master key for the Biology Department that opens both the classroom and the office doors. This is similar to ACh that binds to both types of receptors. The molecules that define these receptors are not crucial—they are simply tools for researchers to use in the laboratory. These molecules are **exogenous**, meaning that they are made outside of the human body, so a researcher can

use them without any confounding **endogenous** results (results caused by the molecules produced in the body).

The adrenergic system also has two types of receptors, named the **alpha (α)-adrenergic receptor** and **beta (β)-adrenergic receptor**. Unlike cholinergic receptors, these receptor types are not classified by which drugs can bind to them. All of them are G protein–coupled receptors. There are three types of α -adrenergic receptors, termed α_1 , α_2 , and α_3 , and there are two types of β -adrenergic receptors, termed β_1 and β_2 . An additional aspect of the adrenergic system is that there is a second signaling molecule called **epinephrine**. The chemical difference between norepinephrine and epinephrine is the addition of a methyl group (CH_3) in epinephrine. The prefix “nor-” actually refers to this chemical difference, in which a methyl group is missing.

The term adrenergic should remind you of the word adrenaline, which is associated with the fight-or-flight response described at the beginning of the chapter. Adrenaline and epinephrine are two names for the same molecule. The adrenal gland (in Latin, ad- = “on top of”; renal = “kidney”) secretes adrenaline. The ending “-ine” refers to the chemical being derived, or extracted, from the adrenal gland. A similar construction from Greek instead of Latin results in the word epinephrine (epi- = “above”; nephro- = “kidney”). In scientific usage, epinephrine is preferred in the United States, whereas adrenaline is preferred in Great Britain, because “adrenalin” was once a registered, proprietary drug name in the United States. Though the drug is no longer sold, the convention of referring to this molecule by the two different names persists. Similarly, norepinephrine and noradrenaline are two names for the same molecule.

Having understood the cholinergic and adrenergic systems, their role in the autonomic system is relatively simple to understand. All preganglionic fibers, both sympathetic and parasympathetic, release ACh. All ganglionic neurons—the targets of these preganglionic fibers—have nicotinic receptors in their cell membranes. The nicotinic receptor is a ligand-gated cation channel that results in depolarization of the postsynaptic membrane. The postganglionic parasympathetic fibers also release ACh, but the receptors on their targets are muscarinic receptors, which are G protein–coupled

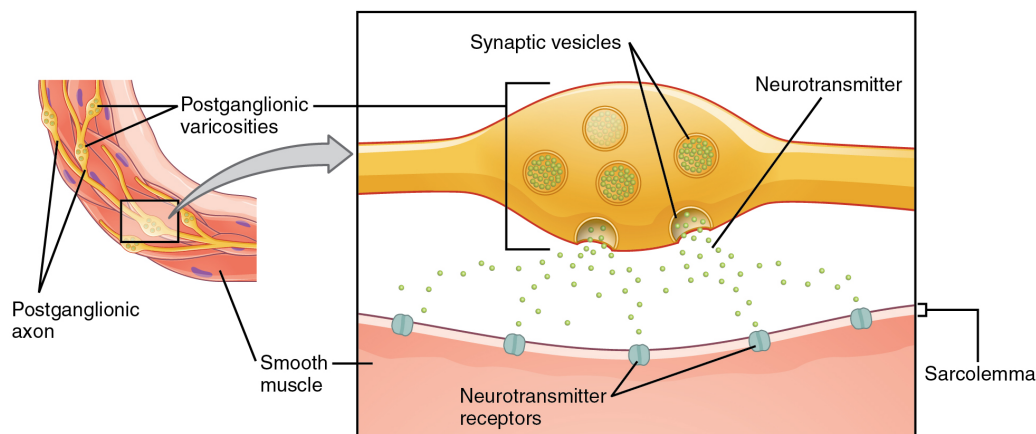
receptors and do not exclusively cause depolarization of the postsynaptic membrane. Postganglionic sympathetic fibers release norepinephrine, except for fibers that project to sweat glands and to blood vessels associated with skeletal muscles, which release ACh ([\[link\]](#)).

| Autonomic System Signaling Molecules | | |
|--------------------------------------|--|-------------------------------------|
| | Sympathetic | Parasympathetic |
| Preganglionic | Acetylcholine → nicotinic receptor | Acetylcholine → nicotinic receptor |
| Postganglionic | Norepinephrine → α - or β -adrenergic receptors Acetylcholine → muscarinic receptor (associated with sweat glands and the blood vessels associated with skeletal muscles only) | Acetylcholine → muscarinic receptor |

Signaling molecules can belong to two broad groups. Neurotransmitters are released at synapses, whereas hormones are released into the bloodstream. These are simplistic definitions, but they can help to clarify this point. Acetylcholine can be considered a neurotransmitter because it is released by axons at synapses. The adrenergic system, however, presents a challenge. Postganglionic sympathetic fibers release norepinephrine, which can be considered a neurotransmitter. But the adrenal medulla releases epinephrine and norepinephrine into circulation, so they should be considered hormones.

What are referred to here as synapses may not fit the strictest definition of synapse. Some sources will refer to the connection between a postganglionic fiber and a target effector as neuroeffector junctions; neurotransmitters, as defined above, would be called neuromodulators. The structure of postganglionic connections are not the typical synaptic end bulb that is found at the neuromuscular junction, but rather are chains of swellings along the length of a postganglionic fiber called a **varicosity** ([\[link\]](#)).

Autonomic Varicosities



The connection between autonomic fibers and target effectors is not the same as the typical synapse, such as the neuromuscular junction. Instead of a synaptic end bulb, a neurotransmitter is released from swellings along the length of a fiber that makes an extended network of connections in the target effector.

Note:

Everyday Connections

Fight or Flight? What About Fright and Freeze?

The original usage of the epithet “fight or flight” comes from a scientist named Walter Cannon who worked at Harvard in 1915. The concept of homeostasis and the functioning of the sympathetic system had been

introduced in France in the previous century. Cannon expanded the idea, and introduced the idea that an animal responds to a threat by preparing to stand and fight or run away. The nature of this response was thoroughly explained in a book on the physiology of pain, hunger, fear, and rage. When students learn about the sympathetic system and the fight-or-flight response, they often stop and wonder about other responses. If you were faced with a lioness running toward you as pictured at the beginning of this chapter, would you run or would you stand your ground? Some people would say that they would freeze and not know what to do. So isn't there really more to what the autonomic system does than fight, flight, rest, or digest. What about fear and paralysis in the face of a threat? The common epithet of "fight or flight" is being enlarged to be "fight, flight, or fright" or even "fight, flight, fright, or freeze." Cannon's original contribution was a catchy phrase to express some of what the nervous system does in response to a threat, but it is incomplete. The sympathetic system is responsible for the physiological responses to emotional states. The name "sympathetic" can be said to mean that (sym- = "together"; -pathos = "pain," "suffering," or "emotion").

Note:



Watch this [video](#) to learn more about the nervous system. As described in this video, the nervous system has a way to deal with threats and stress that is separate from the conscious control of the somatic nervous system. The system comes from a time when threats were about survival, but in the modern age, these responses become part of stress and anxiety. This video describes how the autonomic system is only part of the response to threats, or stressors. What other organ system gets involved, and what part of the

brain coordinates the two systems for the entire response, including epinephrine (adrenaline) and cortisol?

Chapter Review

The primary responsibilities of the autonomic nervous system are to regulate homeostatic mechanisms in the body, which is also part of what the endocrine system does. The key to understanding the autonomic system is to explore the response pathways—the output of the nervous system. The way we respond to the world around us, to manage the internal environment on the basis of the external environment, is divided between two parts of the autonomic nervous system. The sympathetic division responds to threats and produces a readiness to confront the threat or to run away: the fight-or-flight response. The parasympathetic division plays the opposite role. When the external environment does not present any immediate danger, a restful mode descends on the body, and the digestive system is more active.

The sympathetic output of the nervous system originates out of the lateral horn of the thoracolumbar spinal cord. An axon from one of these central neurons projects by way of the ventral spinal nerve root and spinal nerve to a sympathetic ganglion, either in the sympathetic chain ganglia or one of the collateral locations, where it synapses on a ganglionic neuron. These preganglionic fibers release ACh, which excites the ganglionic neuron through the nicotinic receptor. The axon from the ganglionic neuron—the postganglionic fiber—then projects to a target effector where it will release norepinephrine to bind to an adrenergic receptor, causing a change in the physiology of that organ in keeping with the broad, divergent sympathetic response. The postganglionic connections to sweat glands in the skin and blood vessels supplying skeletal muscle are, however, exceptions; those fibers release ACh onto muscarinic receptors. The sympathetic system has a specialized preganglionic connection to the adrenal medulla that causes epinephrine and norepinephrine to be released into the bloodstream rather than exciting a neuron that contacts an organ directly. This hormonal component means that the sympathetic chemical signal can spread throughout the body very quickly and affect many organ systems at once.

The parasympathetic output is based in the brain stem and sacral spinal cord. Neurons from particular nuclei in the brain stem or from the lateral horn of the sacral spinal cord (preganglionic neurons) project to terminal (intramural) ganglia located close to or within the wall of target effectors. These preganglionic fibers also release ACh onto nicotinic receptors to excite the ganglionic neurons. The postganglionic fibers then contact the target tissues within the organ to release ACh, which binds to muscarinic receptors to induce rest-and-digest responses.

Signaling molecules utilized by the autonomic nervous system are released from axons and can be considered as either neurotransmitters (when they directly interact with the effector) or as hormones (when they are released into the bloodstream). The same molecule, such as norepinephrine, could be considered either a neurotransmitter or a hormone on the basis of whether it is released from a postganglionic sympathetic axon or from the adrenal gland. The synapses in the autonomic system are not always the typical type of connection first described in the neuromuscular junction. Instead of having synaptic end bulbs at the very end of an axonal fiber, they may have swellings—called varicosities—along the length of a fiber so that it makes a network of connections within the target tissue.

Interactive Link Questions

Exercise:

Problem:

Watch this [video](#) to learn more about adrenaline and the fight-or-flight response. When someone is said to have a rush of adrenaline, the image of bungee jumpers or skydivers usually comes to mind. But adrenaline, also known as epinephrine, is an important chemical in coordinating the body's fight-or-flight response. In this video, you look inside the physiology of the fight-or-flight response, as envisioned for a firefighter. His body's reaction is the result of the sympathetic division of the autonomic nervous system causing system-wide changes as it prepares for extreme responses. What two changes does adrenaline bring about to help the skeletal muscle response?

Solution:

The heart rate increases to send more blood to the muscles, and the liver releases stored glucose to fuel the muscles.

Exercise:**Problem:**

Watch this [video](#) to learn more about the nervous system. As described in this video, the nervous system has a way to deal with threats and stress that is separate from the conscious control of the somatic nervous system. The system comes from a time when threats were about survival, but in the modern age, these responses become part of stress and anxiety. This video describes how the autonomic system is only part of the response to threats, or stressors. What other organ system gets involved, and what part of the brain coordinates the two systems for the entire response, including epinephrine (adrenaline) and cortisol?

Solution:

The endocrine system is also responsible for responses to stress in our lives. The hypothalamus coordinates the autonomic response through projections into the spinal cord and through influence over the pituitary gland, the effective center of the endocrine system.

Review Questions**Exercise:****Problem:**

Which of these physiological changes would *not* be considered part of the sympathetic fight-or-flight response?

- a. increased heart rate
- b. increased sweating

- c. dilated pupils
 - d. increased stomach motility
-

Solution:

D

Exercise:

Problem: Which type of fiber could be considered the longest?

- a. preganglionic parasympathetic
 - b. preganglionic sympathetic
 - c. postganglionic parasympathetic
 - d. postganglionic sympathetic
-

Solution:

A

Exercise:

Problem:

Which signaling molecule is *most likely* responsible for an increase in digestive activity?

- a. epinephrine
 - b. norepinephrine
 - c. acetylcholine
 - d. adrenaline
-

Solution:

C

Exercise:

Problem:

Which of these cranial nerves contains preganglionic parasympathetic fibers?

- a. optic, CN II
- b. facial, CN VII
- c. trigeminal, CN V
- d. hypoglossal, CN XII

Solution:

B

Exercise:**Problem:**

Which of the following is *not* a target of a sympathetic preganglionic fiber?

- a. intermural ganglion
- b. collateral ganglion
- c. adrenal gland
- d. chain ganglion

Solution:

A

Critical Thinking Questions**Exercise:**

Problem:

In the context of a lioness hunting on the savannah, why would the sympathetic system *not* activate the digestive system?

Solution:

Whereas energy is needed for running away from the threat, blood needs to be sent to the skeletal muscles for oxygen supply. The additional fuel, in the form of carbohydrates, probably wouldn't improve the ability to escape the threat as much as the diversion of oxygen-rich blood would hinder it.

Exercise:**Problem:**

A target effector, such as the heart, receives input from the sympathetic and parasympathetic systems. What is the actual difference between the sympathetic and parasympathetic divisions at the level of those connections (i.e., at the synapse)?

Solution:

The postganglionic sympathetic fiber releases norepinephrine, whereas the postganglionic parasympathetic fiber releases acetylcholine. Specific locations in the heart have adrenergic receptors and muscarinic receptors. Which receptors are bound is the signal that determines how the heart responds.

Glossary

alpha (α)-adrenergic receptor

one of the receptors to which epinephrine and norepinephrine bind, which comes in three subtypes: α_1 , α_2 , and α_3

acetylcholine (ACh)

neurotransmitter that binds at a motor end-plate to trigger depolarization

adrenal medulla

interior portion of the adrenal (or suprarenal) gland that releases epinephrine and norepinephrine into the bloodstream as hormones

adrenergic

synapse where norepinephrine is released, which binds to α - or β -adrenergic receptors

beta (β)-adrenergic receptor

one of the receptors to which epinephrine and norepinephrine bind, which comes in two subtypes: β_1 and β_2

celiac ganglion

one of the collateral ganglia of the sympathetic system that projects to the digestive system

central neuron

specifically referring to the cell body of a neuron in the autonomic system that is located in the central nervous system, specifically the lateral horn of the spinal cord or a brain stem nucleus

cholinergic

synapse at which acetylcholine is released and binds to the nicotinic or muscarinic receptor

chromaffin cells

neuroendocrine cells of the adrenal medulla that release epinephrine and norepinephrine into the bloodstream as part of sympathetic system activity

ciliary ganglion

one of the terminal ganglia of the parasympathetic system, located in the posterior orbit, axons from which project to the iris

collateral ganglia

ganglia outside of the sympathetic chain that are targets of sympathetic preganglionic fibers, which are the celiac, inferior mesenteric, and superior mesenteric ganglia

craniosacral system

alternate name for the parasympathetic division of the autonomic nervous system that is based on the anatomical location of central neurons in brain-stem nuclei and the lateral horn of the sacral spinal cord; also referred to as craniosacral outflow

dorsal nucleus of the vagus nerve

location of parasympathetic neurons that project through the vagus nerve to terminal ganglia in the thoracic and abdominal cavities

Eddinger–Westphal nucleus

location of parasympathetic neurons that project to the ciliary ganglion

endogenous

describes substance made in the human body

epinephrine

signaling molecule released from the adrenal medulla into the bloodstream as part of the sympathetic response

exogenous

describes substance made outside of the human body

fight-or-flight response

set of responses induced by sympathetic activity that lead to either fleeing a threat or standing up to it, which in the modern world is often associated with anxious feelings

G protein–coupled receptor

membrane protein complex that consists of a receptor protein that binds to a signaling molecule—a G protein—that is activated by that binding and in turn activates an effector protein (enzyme) that creates a second-messenger molecule in the cytoplasm of the target cell

ganglionic neuron

specifically refers to the cell body of a neuron in the autonomic system that is located in a ganglion

gray rami communicantes

(singular = ramus communicans) unmyelinated structures that provide a short connection from a sympathetic chain ganglion to the spinal nerve that contains the postganglionic sympathetic fiber

greater splanchnic nerve

nerve that contains fibers of the central sympathetic neurons that do not synapse in the chain ganglia but project onto the celiac ganglion

inferior mesenteric ganglion

one of the collateral ganglia of the sympathetic system that projects to the digestive system

intramural ganglia

terminal ganglia of the parasympathetic system that are found within the walls of the target effector

lesser splanchnic nerve

nerve that contains fibers of the central sympathetic neurons that do not synapse in the chain ganglia but project onto the inferior mesenteric ganglion

ligand-gated cation channel

ion channel, such as the nicotinic receptor, that is specific to positively charged ions and opens when a molecule such as a neurotransmitter binds to it

mesenteric plexus

nervous tissue within the wall of the digestive tract that contains neurons that are the targets of autonomic preganglionic fibers and that project to the smooth muscle and glandular tissues in the digestive organ

muscarinic receptor

type of acetylcholine receptor protein that is characterized by also binding to muscarine and is a metabotropic receptor

nicotinic receptor

type of acetylcholine receptor protein that is characterized by also binding to nicotine and is an ionotropic receptor

norepinephrine

signaling molecule released as a neurotransmitter by most postganglionic sympathetic fibers as part of the sympathetic response, or as a hormone into the bloodstream from the adrenal medulla

nucleus ambiguus

brain-stem nucleus that contains neurons that project through the vagus nerve to terminal ganglia in the thoracic cavity; specifically associated with the heart

parasympathetic division

division of the autonomic nervous system responsible for restful and digestive functions

paravertebral ganglia

autonomic ganglia superior to the sympathetic chain ganglia

postganglionic fiber

axon from a ganglionic neuron in the autonomic nervous system that projects to and synapses with the target effector; sometimes referred to as a postganglionic neuron

preganglionic fiber

axon from a central neuron in the autonomic nervous system that projects to and synapses with a ganglionic neuron; sometimes referred to as a preganglionic neuron

prevertebral ganglia

autonomic ganglia that are anterior to the vertebral column and functionally related to the sympathetic chain ganglia

rest and digest

set of functions associated with the parasympathetic system that lead to restful actions and digestion

superior cervical ganglion

one of the paravertebral ganglia of the sympathetic system that projects to the head

superior mesenteric ganglion

one of the collateral ganglia of the sympathetic system that projects to the digestive system

sympathetic chain ganglia

series of ganglia adjacent to the vertebral column that receive input from central sympathetic neurons

sympathetic division

division of the autonomic nervous system associated with the fight-or-flight response

target effector

organ, tissue, or gland that will respond to the control of an autonomic or somatic or endocrine signal

terminal ganglia

ganglia of the parasympathetic division of the autonomic system, which are located near or within the target effector, the latter also known as intramural ganglia

thoracolumbar system

alternate name for the sympathetic division of the autonomic nervous system that is based on the anatomical location of central neurons in the lateral horn of the thoracic and upper lumbar spinal cord

varicosity

structure of some autonomic connections that is not a typical synaptic end bulb, but a string of swellings along the length of a fiber that makes a network of connections with the target effector

white rami communicantes

(singular = ramus communicans) myelinated structures that provide a short connection from a sympathetic chain ganglion to the spinal nerve that contains the preganglionic sympathetic fiber

Autonomic Reflexes and Homeostasis

By the end of this section, you will be able to:

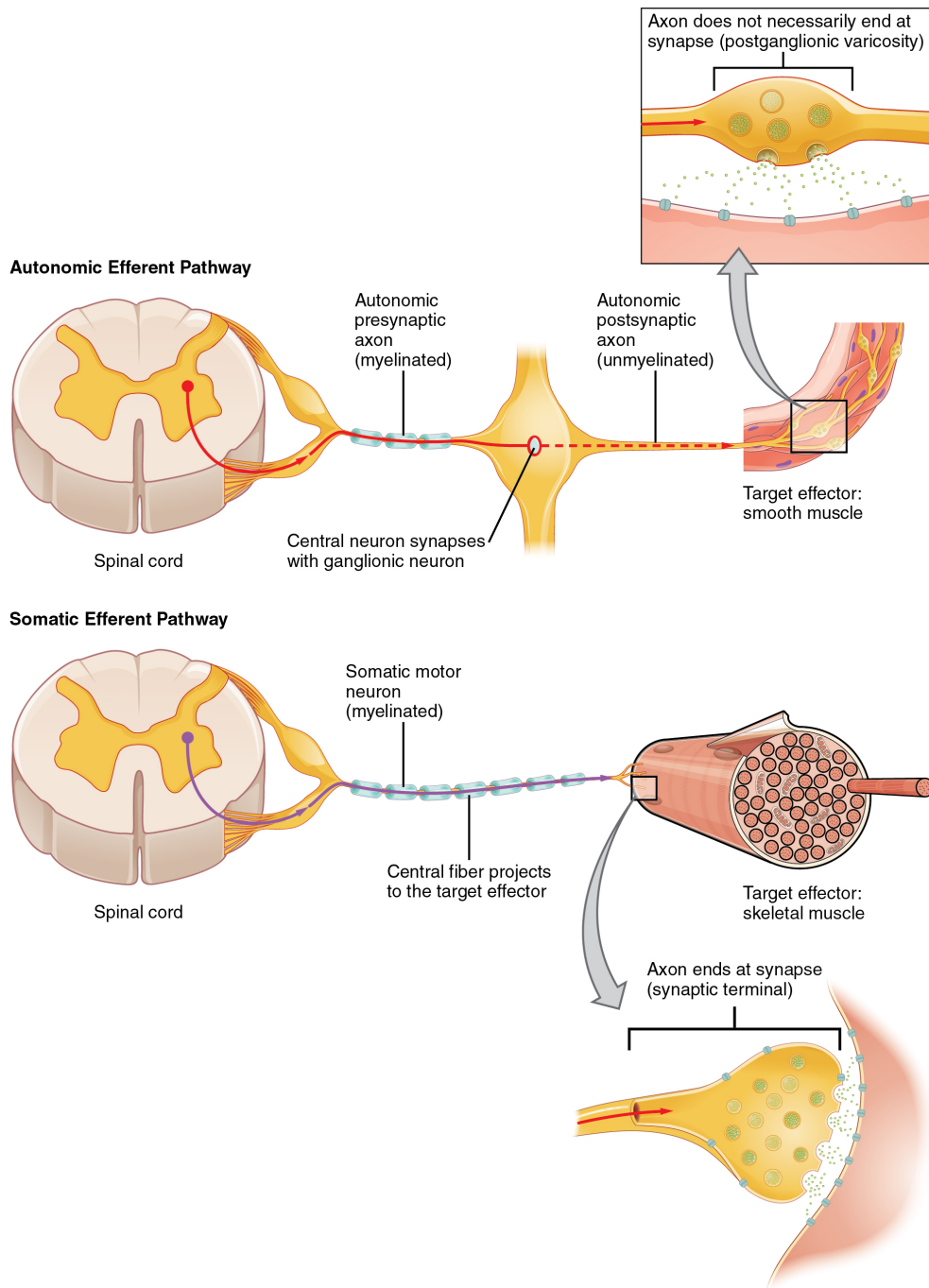
- Compare the structure of somatic and autonomic reflex arcs
- Explain the differences in sympathetic and parasympathetic reflexes
- Differentiate between short and long reflexes
- Determine the effect of the autonomic nervous system on the regulation of the various organ systems on the basis of the signaling molecules involved
- Describe the effects of drugs that affect autonomic function

The autonomic nervous system regulates organ systems through circuits that resemble the reflexes described in the somatic nervous system. The main difference between the somatic and autonomic systems is in what target tissues are effectors. Somatic responses are solely based on skeletal muscle contraction. The autonomic system, however, targets cardiac and smooth muscle, as well as glandular tissue. Whereas the basic circuit is a **reflex arc**, there are differences in the structure of those reflexes for the somatic and autonomic systems.

The Structure of Reflexes

One difference between a **somatic reflex**, such as the withdrawal reflex, and a **visceral reflex**, which is an autonomic reflex, is in the **efferent branch**. The output of a somatic reflex is the lower motor neuron in the ventral horn of the spinal cord that projects directly to a skeletal muscle to cause its contraction. The output of a visceral reflex is a two-step pathway starting with the preganglionic fiber emerging from a lateral horn neuron in the spinal cord, or a cranial nucleus neuron in the brain stem, to a ganglion—followed by the postganglionic fiber projecting to a target effector. The other part of a reflex, the **afferent branch**, is often the same between the two systems. Sensory neurons receiving input from the periphery—with cell bodies in the sensory ganglia, either of a cranial nerve or a dorsal root ganglion adjacent to the spinal cord—project into the CNS to initiate the reflex ([\[link\]](#)). The Latin root “effere” means “to carry.” Adding the prefix “ef-” suggests the meaning “to carry away,” whereas adding the prefix “af-” suggests “to carry toward or inward.”

Comparison of Somatic and Visceral Reflexes



The afferent inputs to somatic and visceral reflexes are essentially the same, whereas the efferent branches are different. Somatic reflexes, for instance, involve a direct connection from the ventral horn of the spinal cord to the skeletal muscle. Visceral reflexes involve a projection

from the central neuron to a ganglion, followed by a second projection from the ganglion to the target effector.

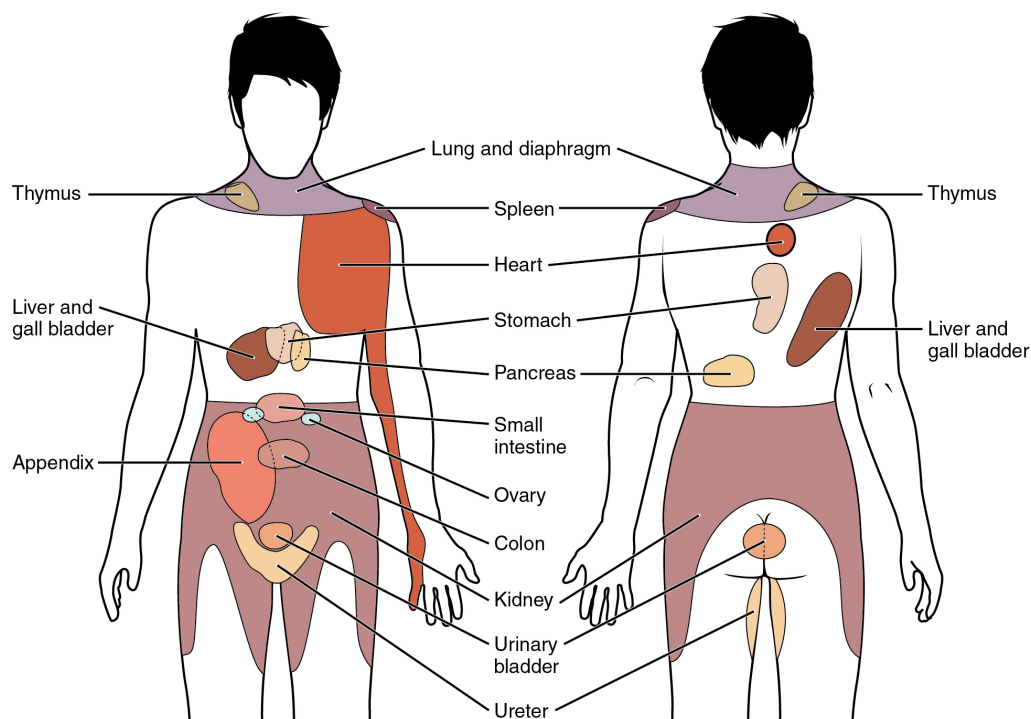
Afferent Branch

The afferent branch of a reflex arc does differ between somatic and visceral reflexes in some instances. Many of the inputs to visceral reflexes are from special or somatic senses, but particular senses are associated with the viscera that are not part of the conscious perception of the environment through the somatic nervous system. For example, there is a specific type of mechanoreceptor, called a **baroreceptor**, in the walls of the aorta and carotid sinuses that senses the stretch of those organs when blood volume or pressure increases. You do not have a conscious perception of having high blood pressure, but that is an important afferent branch of the cardiovascular and, particularly, vasomotor reflexes. The sensory neuron is essentially the same as any other general sensory neuron. The baroreceptor apparatus is part of the ending of a unipolar neuron that has a cell body in a sensory ganglion. The baroreceptors from the carotid arteries have axons in the glossopharyngeal nerve, and those from the aorta have axons in the vagus nerve.

Though visceral senses are not primarily a part of conscious perception, those sensations sometimes make it to conscious awareness. If a visceral sense is strong enough, it will be perceived. The sensory homunculus—the representation of the body in the primary somatosensory cortex—only has a small region allotted for the perception of internal stimuli. If you swallow a large bolus of food, for instance, you will probably feel the lump of that food as it pushes through your esophagus, or even if your stomach is distended after a large meal. If you inhale especially cold air, you can feel it as it enters your larynx and trachea. These sensations are not the same as feeling high blood pressure or blood sugar levels.

When particularly strong visceral sensations rise to the level of conscious perception, the sensations are often felt in unexpected places. For example, strong visceral sensations of the heart will be felt as pain in the left shoulder and left arm. This irregular pattern of projection of conscious perception of visceral sensations is called **referred pain**. Depending on the organ system affected, the referred pain will project to different areas of the body ([link](#)). The location of referred pain is not random, but a definitive explanation of the mechanism has not been established. The most broadly accepted theory for this phenomenon is that the visceral sensory fibers enter into the same level of the spinal cord as the somatosensory fibers of the referred pain location. By this explanation, the visceral sensory fibers from the mediastinal region, where the heart is located, would enter the spinal cord at the same level as the spinal nerves from the shoulder and arm, so the brain misinterprets the sensations from the mediastinal region as being from the axillary and brachial regions. Projections from the medial and inferior divisions of the cervical ganglia do enter the spinal cord at the middle to lower cervical levels, which is where the somatosensory fibers enter.

Referred Pain Chart



Conscious perception of visceral sensations map to specific regions of the body, as shown in this chart. Some sensations

are felt locally, whereas others are perceived as affecting areas that are quite distant from the involved organ.

Note:

Disorders of the...

Nervous System: Kehr's Sign

Kehr's sign is the presentation of pain in the left shoulder, chest, and neck regions following rupture of the spleen. The spleen is in the upper-left abdominopelvic quadrant, but the pain is more in the shoulder and neck. How can this be? The sympathetic fibers connected to the spleen are from the celiac ganglion, which would be from the mid-thoracic to lower thoracic region whereas parasympathetic fibers are found in the vagus nerve, which connects in the medulla of the brain stem. However, the neck and shoulder would connect to the spinal cord at the mid-cervical level of the spinal cord. These connections do not fit with the expected correspondence of visceral and somatosensory fibers entering at the same level of the spinal cord.

The incorrect assumption would be that the visceral sensations are coming from the spleen directly. In fact, the visceral fibers are coming from the diaphragm. The nerve connecting to the diaphragm takes a special route. The phrenic nerve is connected to the spinal cord at cervical levels 3 to 5. The motor fibers that make up this nerve are responsible for the muscle contractions that drive ventilation. These fibers have left the spinal cord to enter the phrenic nerve, meaning that spinal cord damage below the mid-cervical level is not fatal by making ventilation impossible. Therefore, the visceral fibers from the diaphragm enter the spinal cord at the same level as the somatosensory fibers from the neck and shoulder.

The diaphragm plays a role in Kehr's sign because the spleen is just inferior to the diaphragm in the upper-left quadrant of the abdominopelvic cavity. When the spleen ruptures, blood spills into this region. The accumulating hemorrhage then puts pressure on the diaphragm. The visceral sensation is actually in the diaphragm, so the referred pain is in a region of the body that corresponds to the diaphragm, not the spleen.

Efferent Branch

The efferent branch of the visceral reflex arc begins with the projection from the central neuron along the preganglionic fiber. This fiber then makes a synapse on the ganglionic neuron that projects to the target effector.

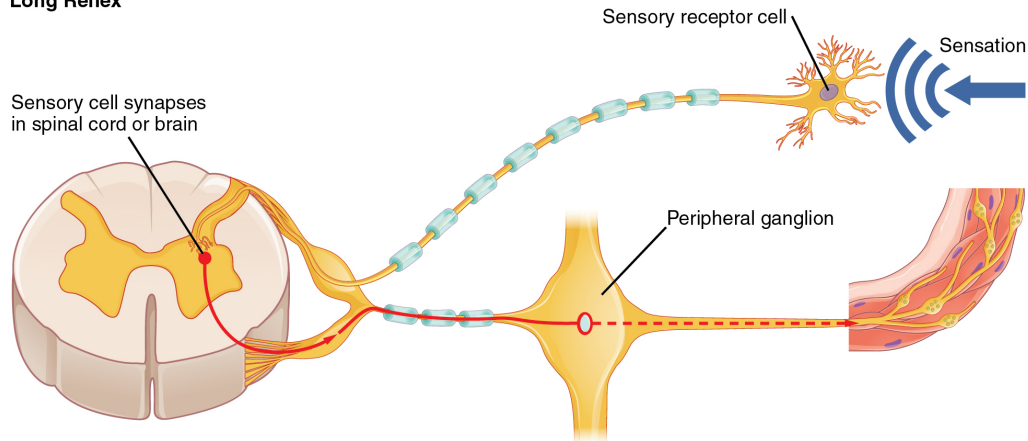
The effector organs that are the targets of the autonomic system range from the iris and ciliary body of the eye to the urinary bladder and reproductive organs. The thoracolumbar output, through the various sympathetic ganglia, reaches all of these organs. The cranial component of the parasympathetic system projects from the eye to part of the intestines. The sacral component picks up with the majority of the large intestine and the pelvic organs of the urinary and reproductive systems.

Short and Long Reflexes

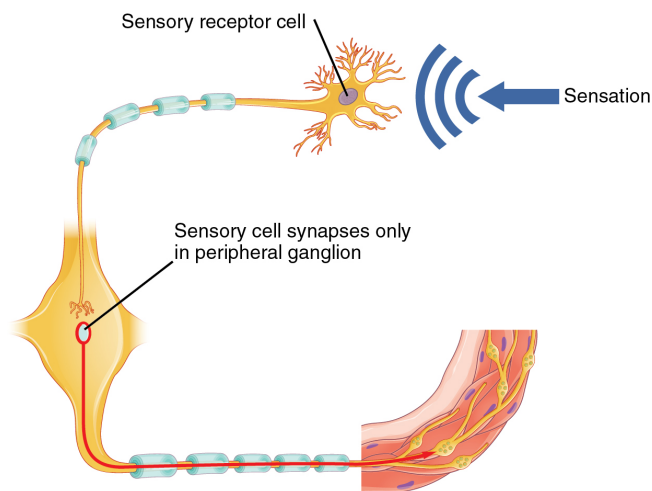
Somatic reflexes involve sensory neurons that connect sensory receptors to the CNS and motor neurons that project back out to the skeletal muscles. Visceral reflexes that involve the thoracolumbar or craniosacral systems share similar connections. However, there are reflexes that do not need to involve any CNS components. A **long reflex** has afferent branches that enter the spinal cord or brain and involve the efferent branches, as previously explained. A **short reflex** is completely peripheral and only involves the local integration of sensory input with motor output ([\[link\]](#)).

Short and Long Reflexes

Long Reflex



Short Reflex



Sensory input can stimulate either a short or a long reflex.

A sensory neuron can project to the CNS or to an autonomic ganglion. The short reflex involves the direct stimulation of a postganglionic fiber by the sensory neuron, whereas the long reflex involves integration in the spinal cord or brain.

The difference between short and long reflexes is in the involvement of the CNS. Somatic reflexes always involve the CNS, even in a monosynaptic reflex in which the sensory neuron directly activates the motor neuron. That synapse is in the spinal cord or brain stem, so it has to involve the CNS. However, in the autonomic system there is the possibility that the CNS is

not involved. Because the efferent branch of a visceral reflex involves two neurons—the central neuron and the ganglionic neuron—a “short circuit” can be possible. If a sensory neuron projects directly to the ganglionic neuron and causes it to activate the effector target, then the CNS is not involved.

A division of the nervous system that is related to the autonomic nervous system is the enteric nervous system. The word enteric refers to the digestive organs, so this represents the nervous tissue that is part of the digestive system. There are a few myenteric plexuses in which the nervous tissue in the wall of the digestive tract organs can directly influence digestive function. If stretch receptors in the stomach are activated by the filling and distension of the stomach, a short reflex will directly activate the smooth muscle fibers of the stomach wall to increase motility to digest the excessive food in the stomach. No CNS involvement is needed because the stretch receptor is directly activating a neuron in the wall of the stomach that causes the smooth muscle to contract. That neuron, connected to the smooth muscle, is a postganglionic parasympathetic neuron that can be controlled by a fiber found in the vagus nerve.

Note:



Read this [article](#) to learn about a teenager who experiences a series of spells that suggest a stroke. He undergoes endless tests and seeks input from multiple doctors. In the end, one expert, one question, and a simple blood pressure cuff answers the question. Why would the heart have to beat faster when the teenager changes his body position from lying down to sitting, and then to standing?

Balance in Competing Autonomic Reflex Arcs

The autonomic nervous system is important for homeostasis because its two divisions compete at the target effector. The balance of homeostasis is attributable to the competing inputs from the sympathetic and parasympathetic divisions (dual innervation). At the level of the target effector, the signal of which system is sending the message is strictly chemical. A signaling molecule binds to a receptor that causes changes in the target cell, which in turn causes the tissue or organ to respond to the changing conditions of the body.

Competing Neurotransmitters

The postganglionic fibers of the sympathetic and parasympathetic divisions both release neurotransmitters that bind to receptors on their targets. Postganglionic sympathetic fibers release norepinephrine, with a minor exception, whereas postganglionic parasympathetic fibers release ACh. For any given target, the difference in which division of the autonomic nervous system is exerting control is just in what chemical binds to its receptors. The target cells will have adrenergic and muscarinic receptors. If norepinephrine is released, it will bind to the adrenergic receptors present on the target cell, and if ACh is released, it will bind to the muscarinic receptors on the target cell.

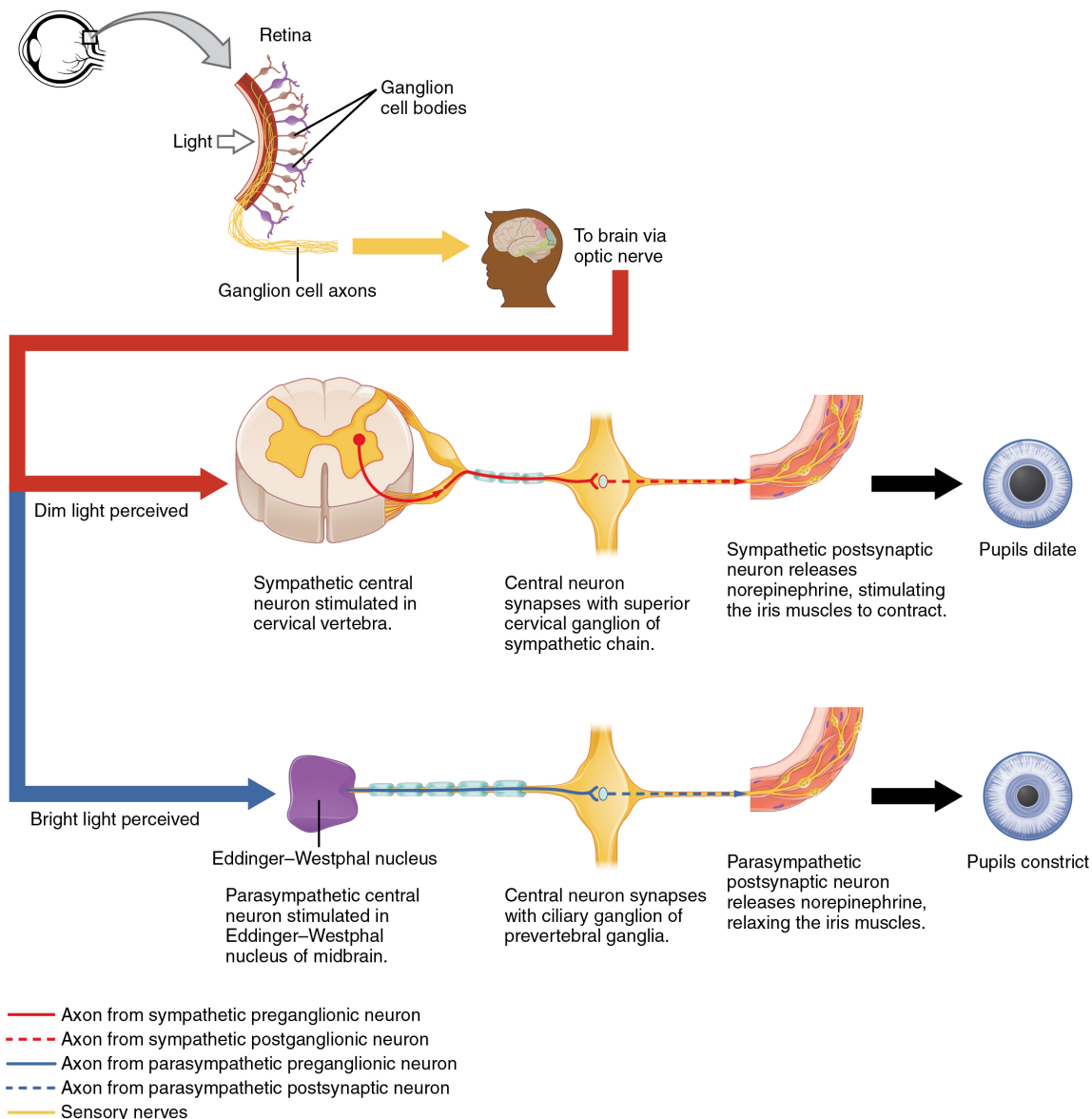
In the sympathetic system, there are exceptions to this pattern of dual innervation. The postganglionic sympathetic fibers that contact the blood vessels within skeletal muscle and that contact sweat glands do not release norepinephrine, they release ACh. This does not create any problem because there is no parasympathetic input to the sweat glands. Sweat glands have muscarinic receptors and produce and secrete sweat in response to the presence of ACh.

At most of the other targets of the autonomic system, the effector response is based on which neurotransmitter is released and what receptor is present. For example, regions of the heart that establish heart rate are contacted by postganglionic fibers from both systems. If norepinephrine is released onto

those cells, it binds to an adrenergic receptor that causes the cells to depolarize faster, and the heart rate increases. If ACh is released onto those cells, it binds to a muscarinic receptor that causes the cells to hyperpolarize so that they cannot reach threshold as easily, and the heart rate slows. Without this parasympathetic input, the heart would work at a rate of approximately 100 beats per minute (bpm). The sympathetic system speeds that up, as it would during exercise, to 120–140 bpm, for example. The parasympathetic system slows it down to the resting heart rate of 60–80 bpm.

Another example is in the control of pupillary size ([link](#)). The afferent branch responds to light hitting the retina. Photoreceptors are activated, and the signal is transferred to the retinal ganglion cells that send an action potential along the optic nerve into the diencephalon. If light levels are low, the sympathetic system sends a signal out through the upper thoracic spinal cord to the superior cervical ganglion of the sympathetic chain. The postganglionic fiber then projects to the iris, where it releases norepinephrine onto the radial fibers of the iris (a smooth muscle). When those fibers contract, the pupil dilates—increasing the amount of light hitting the retina. If light levels are too high, the parasympathetic system sends a signal out from the Edinger–Westphal nucleus through the oculomotor nerve. This fiber synapses in the ciliary ganglion in the posterior orbit. The postganglionic fiber then projects to the iris, where it releases ACh onto the circular fibers of the iris—another smooth muscle. When those fibers contract, the pupil constricts to limit the amount of light hitting the retina.

Autonomic Control of Pupillary Size



Activation of the pupillary reflex comes from the amount of light activating the retinal ganglion cells, as sent along the optic nerve. The output of the sympathetic system projects through the superior cervical ganglion, whereas the parasympathetic system originates out of the midbrain and projects through the oculomotor nerve to the ciliary ganglion, which then projects to the iris. The postganglionic fibers of either division release neurotransmitters onto the smooth muscles of the iris to cause changes in the pupillary size. Norepinephrine results in dilation and ACh results in constriction.

In this example, the autonomic system is controlling how much light hits the retina. It is a homeostatic reflex mechanism that keeps the activation of photoreceptors within certain limits. In the context of avoiding a threat like the lioness on the savannah, the sympathetic response for fight or flight will increase pupillary diameter so that more light hits the retina and more visual information is available for running away. Likewise, the parasympathetic response of rest reduces the amount of light reaching the retina, allowing the photoreceptors to cycle through bleaching and be regenerated for further visual perception; this is what the homeostatic process is attempting to maintain.

Note:



Watch this [video](#) to learn about the pupillary reflexes. The pupillary light reflex involves sensory input through the optic nerve and motor response through the oculomotor nerve to the ciliary ganglion, which projects to the circular fibers of the iris. As shown in this short animation, pupils will constrict to limit the amount of light falling on the retina under bright lighting conditions. What constitutes the afferent and efferent branches of the competing reflex (dilation)?

Autonomic Tone

Organ systems are balanced between the input from the sympathetic and parasympathetic divisions. When something upsets that balance, the

homeostatic mechanisms strive to return it to its regular state. For each organ system, there may be more of a sympathetic or parasympathetic tendency to the resting state, which is known as the **autonomic tone** of the system. For example, the heart rate was described above. Because the resting heart rate is the result of the parasympathetic system slowing the heart down from its intrinsic rate of 100 bpm, the heart can be said to be in parasympathetic tone.

In a similar fashion, another aspect of the cardiovascular system is primarily under sympathetic control. Blood pressure is partially determined by the contraction of smooth muscle in the walls of blood vessels. These tissues have adrenergic receptors that respond to the release of norepinephrine from postganglionic sympathetic fibers by constricting and increasing blood pressure. The hormones released from the adrenal medulla—epinephrine and norepinephrine—will also bind to these receptors. Those hormones travel through the bloodstream where they can easily interact with the receptors in the vessel walls. The parasympathetic system has no significant input to the systemic blood vessels, so the sympathetic system determines their tone.

There are a limited number of blood vessels that respond to sympathetic input in a different fashion. Blood vessels in skeletal muscle, particularly those in the lower limbs, are more likely to dilate. It does not have an overall effect on blood pressure to alter the tone of the vessels, but rather allows for blood flow to increase for those skeletal muscles that will be active in the fight-or-flight response. The blood vessels that have a parasympathetic projection are limited to those in the erectile tissue of the reproductive organs. Acetylcholine released by these postganglionic parasympathetic fibers cause the vessels to dilate, leading to the engorgement of the erectile tissue.

Note:**Homeostatic Imbalances****Orthostatic Hypotension**

Have you ever stood up quickly and felt dizzy for a moment? This is because, for one reason or another, blood is not getting to your brain so it is

briefly deprived of oxygen. When you change position from sitting or lying down to standing, your cardiovascular system has to adjust for a new challenge, keeping blood pumping up into the head while gravity is pulling more and more blood down into the legs.

The reason for this is a sympathetic reflex that maintains the output of the heart in response to postural change. When a person stands up, proprioceptors indicate that the body is changing position. A signal goes to the CNS, which then sends a signal to the upper thoracic spinal cord neurons of the sympathetic division. The sympathetic system then causes the heart to beat faster and the blood vessels to constrict. Both changes will make it possible for the cardiovascular system to maintain the rate of blood delivery to the brain. Blood is being pumped superiorly through the internal branch of the carotid arteries into the brain, against the force of gravity. Gravity is not increasing while standing, but blood is more likely to flow down into the legs as they are extended for standing. This sympathetic reflex keeps the brain well oxygenated so that cognitive and other neural processes are not interrupted.

Sometimes this does not work properly. If the sympathetic system cannot increase cardiac output, then blood pressure into the brain will decrease, and a brief neurological loss can be felt. This can be brief, as a slight “wooziness” when standing up too quickly, or a loss of balance and neurological impairment for a period of time. The name for this is orthostatic hypotension, which means that blood pressure goes below the homeostatic set point when standing. It can be the result of standing up faster than the reflex can occur, which may be referred to as a benign “head rush,” or it may be the result of an underlying cause.

There are two basic reasons that orthostatic hypotension can occur. First, blood volume is too low and the sympathetic reflex is not effective. This hypovolemia may be the result of dehydration or medications that affect fluid balance, such as diuretics or vasodilators. Both of these medications are meant to lower blood pressure, which may be necessary in the case of systemic hypertension, and regulation of the medications may alleviate the problem. Sometimes increasing fluid intake or water retention through salt intake can improve the situation.

The second underlying cause of orthostatic hypotension is autonomic failure. There are several disorders that result in compromised sympathetic functions. The disorders range from diabetes to multiple system atrophy (a

loss of control over many systems in the body), and addressing the underlying condition can improve the hypotension. For example, with diabetes, peripheral nerve damage can occur, which would affect the postganglionic sympathetic fibers. Getting blood glucose levels under control can improve neurological deficits associated with diabetes.

Chapter Review

Autonomic nervous system function is based on the visceral reflex. This reflex is similar to the somatic reflex, but the efferent branch is composed of two neurons. The central neuron projects from the spinal cord or brain stem to synapse on the ganglionic neuron that projects to the effector. The afferent branch of the somatic and visceral reflexes is very similar, as many somatic and special senses activate autonomic responses. However, there are visceral senses that do not form part of conscious perception. If a visceral sensation, such as cardiac pain, is strong enough, it will rise to the level of consciousness. However, the sensory homunculus does not provide a representation of the internal structures to the same degree as the surface of the body, so visceral sensations are often experienced as referred pain, such as feelings of pain in the left shoulder and arm in connection with a heart attack.

The role of visceral reflexes is to maintain a balance of function in the organ systems of the body. The two divisions of the autonomic system each play a role in effecting change, usually in competing directions. The sympathetic system increases heart rate, whereas the parasympathetic system decreases heart rate. The sympathetic system dilates the pupil of the eye, whereas the parasympathetic system constricts the pupil. The competing inputs can contribute to the resting tone of the organ system. Heart rate is normally under parasympathetic tone, whereas blood pressure is normally under sympathetic tone. The heart rate is slowed by the autonomic system at rest, whereas blood vessels retain a slight constriction at rest.

In a few systems of the body, the competing input from the two divisions is not the norm. The sympathetic tone of blood vessels is caused by the lack of

parasympathetic input to the systemic circulatory system. Only certain regions receive parasympathetic input that relaxes the smooth muscle wall of the blood vessels. Sweat glands are another example, which only receive input from the sympathetic system.

Interactive Link Questions

Exercise:

Problem:

Read this [article](#) to learn about a teenager who experiences a series of spells that suggest a stroke. He undergoes endless tests and seeks input from multiple doctors. In the end, one expert, one question, and a simple blood pressure cuff answers the question. Why would the heart have to beat faster when the teenager changes his body position from lying down to sitting, and then to standing?

Solution:

The effect of gravity on circulation means that it is harder to get blood up from the legs as the body takes on a vertical orientation.

Exercise:

Problem:

Watch this [video](#) to learn about the pupillary reflexes. The pupillary light reflex involves sensory input through the optic nerve and motor response through the oculomotor nerve to the ciliary ganglion, which projects to the circular fibers of the iris. As shown in this short animation, pupils will constrict to limit the amount of light falling on the retina under bright lighting conditions. What constitutes the afferent and efferent branches of the competing reflex (dilation)?

Solution:

The optic nerve still carries the afferent input, but the output is from the thoracic spinal cord, through the superior cervical ganglion, to the

radial fibers of the iris.

Review Questions

Exercise:

Problem:

Which of the following represents a sensory input that is *not* part of both the somatic and autonomic systems?

- a. vision
- b. taste
- c. baroreception
- d. proprioception

Solution:

C

Exercise:

Problem:

What is the term for a reflex that does *not* include a CNS component?

- a. long reflex
- b. visceral reflex
- c. somatic reflex
- d. short reflex

Solution:

D

Exercise:

Problem:

What neurotransmitter will result in constriction of the pupil?

- a. norepinephrine
- b. acetylcholine
- c. epinephrine
- d. serotonin

Solution:

B

Exercise:

Problem:

What gland produces a secretion that causes fight-or-flight responses in effectors?

- a. adrenal medulla
- b. salivatory gland
- c. reproductive gland
- d. thymus

Solution:

A

Exercise:

Problem: Which of the following is an incorrect pairing?

- a. norepinephrine dilates the pupil
- b. epinephrine increases blood pressure
- c. acetylcholine decreases digestion
- d. norepinephrine increases heart rate

Solution:

C

Critical Thinking Questions

Exercise:**Problem:**

Damage to internal organs will present as pain associated with a particular surface area of the body. Why would something like irritation to the diaphragm, which is between the thoracic and abdominal cavities, feel like pain in the shoulder or neck?

Solution:

The nerves that carry sensory information from the diaphragm enter the spinal cord in the cervical region where somatic sensory fibers from the shoulder and neck would enter. The brain superimposes this experience onto the sensory homunculus where the somatic nerves are connected.

Exercise:**Problem:**

Medical practice is paying more attention to the autonomic system in considering disease states. Why would autonomic tone be important in considering cardiovascular disease?

Solution:

Within the cardiovascular system, different aspects demonstrate variation in autonomic tone. Heart rate is under parasympathetic tone, and blood pressure is under sympathetic tone. Pharmaceuticals that treat cardiovascular disorders may be more effective if they work with

the normal state of the autonomic system. Alternatively, some disorders may be exacerbated by autonomic deficits and common therapies might not be as effective.

Glossary

autonomic tone

tendency of an organ system to be governed by one division of the autonomic nervous system over the other, such as heart rate being lowered by parasympathetic input at rest

afferent branch

component of a reflex arc that represents the input from a sensory neuron, for either a special or general sense

baroreceptor

mechanoreceptor that senses the stretch of blood vessels to indicate changes in blood pressure

efferent branch

component of a reflex arc that represents the output, with the target being an effector, such as muscle or glandular tissue

long reflex

reflex arc that includes the central nervous system

referred pain

the conscious perception of visceral sensation projected to a different region of the body, such as the left shoulder and arm pain as a sign for a heart attack

reflex arc

circuit of a reflex that involves a sensory input and motor output, or an afferent branch and an efferent branch, and an integrating center to connect the two branches

short reflex

reflex arc that does not include any components of the central nervous system

somatic reflex

reflex involving skeletal muscle as the effector, under the control of the somatic nervous system

visceral reflex

reflex involving an internal organ as the effector, under the control of the autonomic nervous system

Introduction

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The Worldwide AIDS Epidemic

(a) As of 2008, more than 15 percent of adults were infected with HIV in certain African countries.

This grim picture had changed little by

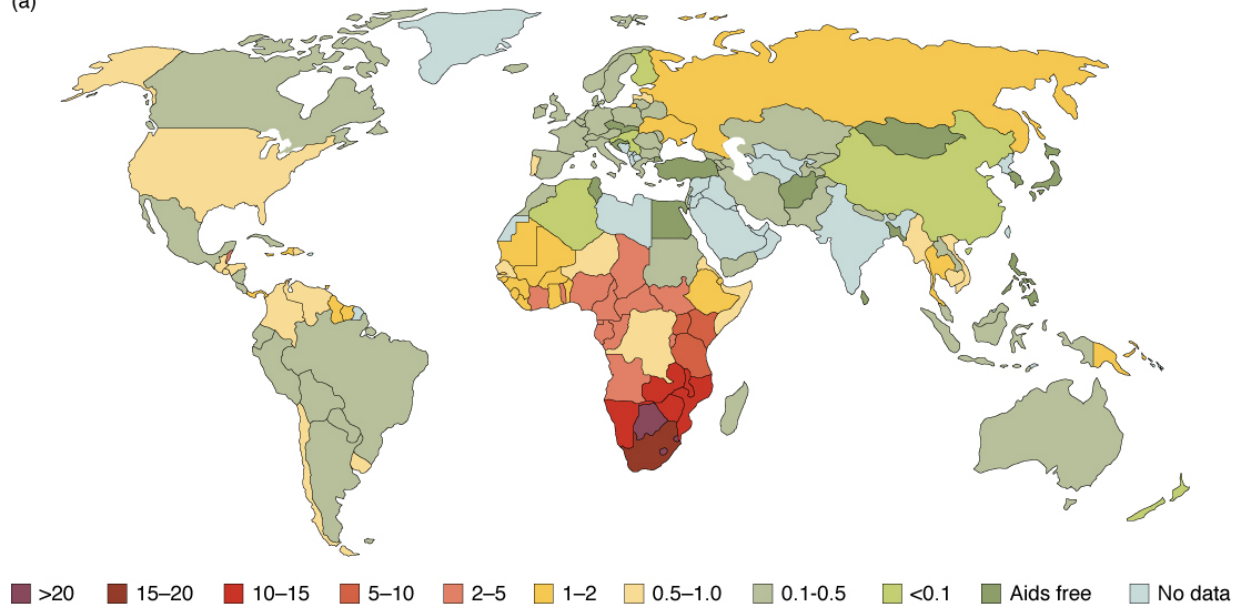
2012. (b) In

this scanning electron micrograph, HIV virions (green particles)

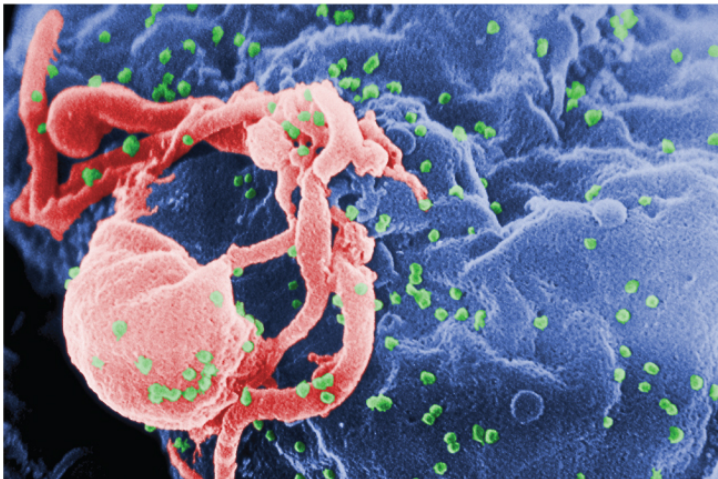
are budding off the surface of a macrophage (pink structure).

(credit b: C. Goldsmith)

(a)



(b)



Note:

Chapter Objectives

After studying this chapter, you will be able to:

- Identify the components and anatomy of the lymphatic system
- Discuss the role of the innate immune response against pathogens
- Describe the power of the adaptive immune response to cure disease
- Explain immunological deficiencies and over-reactions of the immune system

- Discuss the role of the immune response in transplantation and cancer
- Describe the interaction of the immune and lymphatic systems with other body systems

In June 1981, the Centers for Disease Control and Prevention (CDC), in Atlanta, Georgia, published a report of an unusual cluster of five patients in Los Angeles, California. All five were diagnosed with a rare pneumonia caused by a fungus called *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*).

Why was this unusual? Although commonly found in the lungs of healthy individuals, this fungus is an opportunistic pathogen that causes disease in individuals with suppressed or underdeveloped immune systems. The very young, whose immune systems have yet to mature, and the elderly, whose immune systems have declined with age, are particularly susceptible. The five patients from LA, though, were between 29 and 36 years of age and should have been in the prime of their lives, immunologically speaking. What could be going on?

A few days later, a cluster of eight cases was reported in New York City, also involving young patients, this time exhibiting a rare form of skin cancer known as Kaposi's sarcoma. This cancer of the cells that line the blood and lymphatic vessels was previously observed as a relatively innocuous disease of the elderly. The disease that doctors saw in 1981 was frighteningly more severe, with multiple, fast-growing lesions that spread to all parts of the body, including the trunk and face. Could the immune systems of these young patients have been compromised in some way? Indeed, when they were tested, they exhibited extremely low numbers of a specific type of white blood cell in their bloodstreams, indicating that they had somehow lost a major part of the immune system.

Acquired immune deficiency syndrome, or AIDS, turned out to be a new disease caused by the previously unknown human immunodeficiency virus (HIV). Although nearly 100 percent fatal in those with active HIV infections in the early years, the development of anti-HIV drugs has

transformed HIV infection into a chronic, manageable disease and not the certain death sentence it once was. One positive outcome resulting from the emergence of HIV disease was that the public's attention became focused as never before on the importance of having a functional and healthy immune system.

Anatomy of the Lymphatic and Immune Systems

By the end of this section, you will be able to:

- Describe the structure and function of the lymphatic tissue (lymph fluid, vessels, ducts, and organs)
- Describe the structure and function of the primary and secondary lymphatic organs
- Discuss the cells of the immune system, how they function, and their relationship with the lymphatic system

The **immune system** is the complex collection of cells and organs that destroys or neutralizes pathogens that would otherwise cause disease or death. The lymphatic system, for most people, is associated with the immune system to such a degree that the two systems are virtually indistinguishable. The **lymphatic system** is the system of vessels, cells, and organs that carries excess fluids to the bloodstream and filters pathogens from the blood. The swelling of lymph nodes during an infection and the transport of lymphocytes via the lymphatic vessels are but two examples of the many connections between these critical organ systems.

Functions of the Lymphatic System

A major function of the lymphatic system is to drain body fluids and return them to the bloodstream. Blood pressure causes leakage of fluid from the capillaries, resulting in the accumulation of fluid in the interstitial space—that is, spaces between individual cells in the tissues. In humans, 20 liters of plasma is released into the interstitial space of the tissues each day due to capillary filtration. Once this filtrate is out of the bloodstream and in the tissue spaces, it is referred to as interstitial fluid. Of this, 17 liters is reabsorbed directly by the blood vessels. But what happens to the remaining three liters? This is where the lymphatic system comes into play. It drains the excess fluid and empties it back into the bloodstream via a series of vessels, trunks, and ducts. **Lymph** is the term used to describe interstitial fluid once it has entered the lymphatic system. When the lymphatic system is damaged in some way, such as by being blocked by cancer cells or destroyed by injury, protein-rich interstitial fluid accumulates (sometimes “backs up” from the lymph vessels) in the tissue spaces. This inappropriate

accumulation of fluid referred to as lymphedema may lead to serious medical consequences.

As the vertebrate immune system evolved, the network of lymphatic vessels became convenient avenues for transporting the cells of the immune system. Additionally, the transport of dietary lipids and fat-soluble vitamins absorbed in the gut uses this system.

Cells of the immune system not only use lymphatic vessels to make their way from interstitial spaces back into the circulation, but they also use lymph nodes as major staging areas for the development of critical immune responses. A **lymph node** is one of the small, bean-shaped organs located throughout the lymphatic system.

Note:

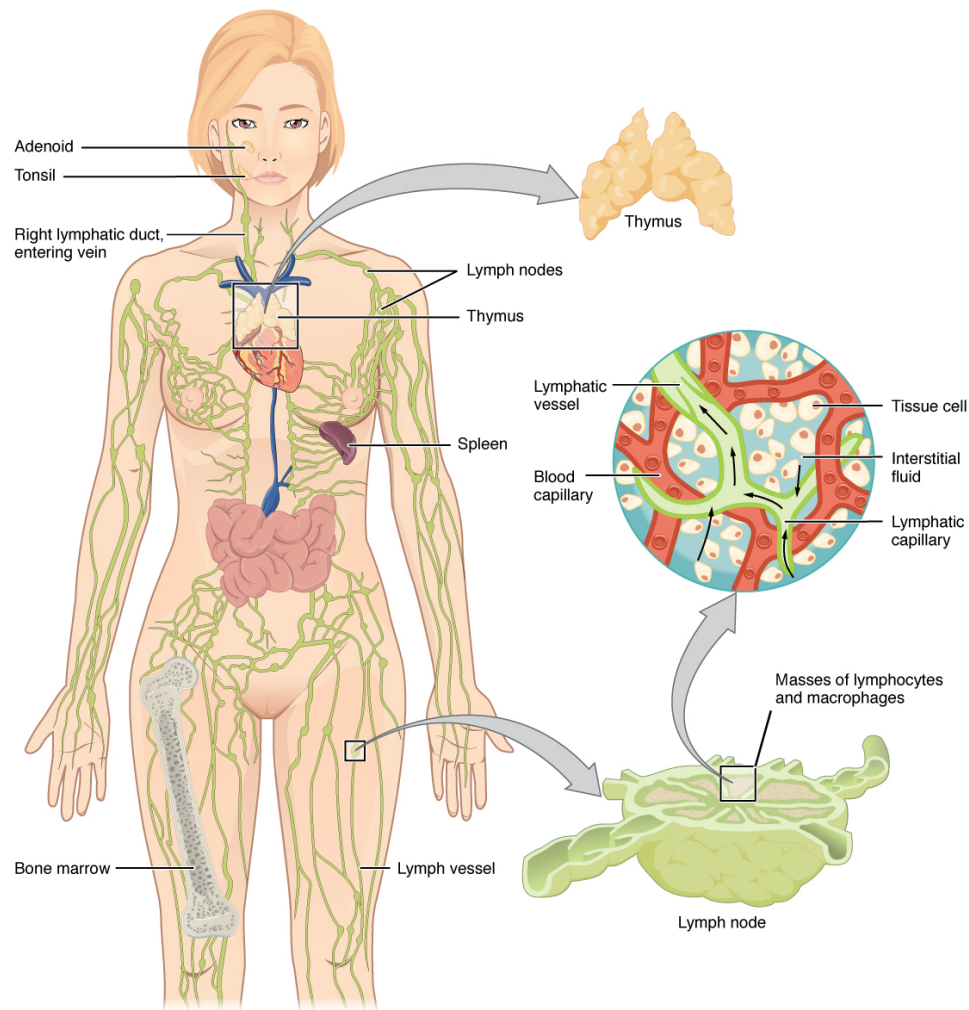


Visit this [website](#) for an overview of the lymphatic system. What are the three main components of the lymphatic system?

Structure of the Lymphatic System

The lymphatic vessels begin as open-ended capillaries, which feed into larger and larger lymphatic vessels, and eventually empty into the bloodstream by a series of ducts. Along the way, the lymph travels through the lymph nodes, which are commonly found near the groin, armpits, neck, chest, and abdomen. Humans have about 500–600 lymph nodes throughout the body ([link](#)).

Anatomy of the Lymphatic System



Lymphatic vessels in the arms and legs convey lymph to the larger lymphatic vessels in the torso.

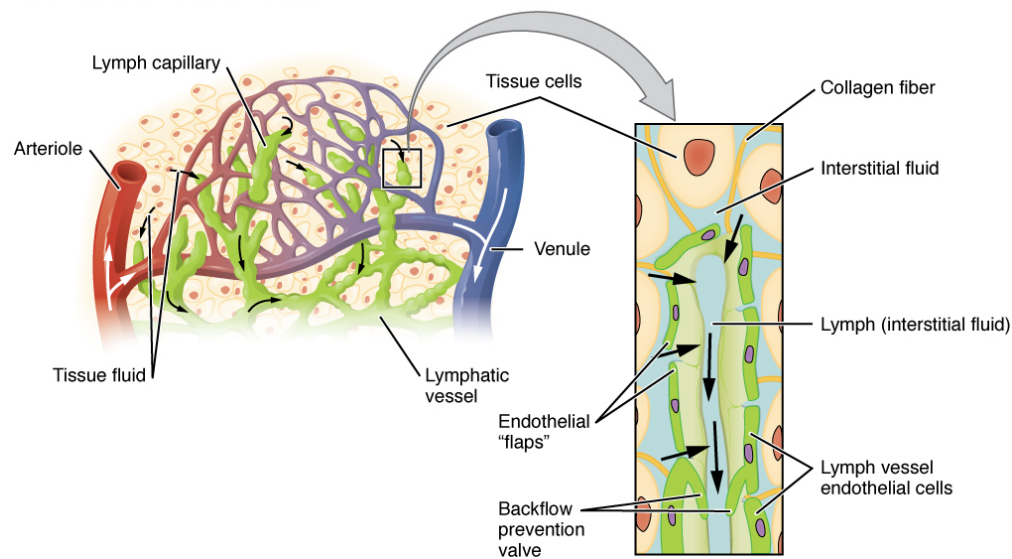
A major distinction between the lymphatic and cardiovascular systems in humans is that lymph is not actively pumped by the heart, but is forced through the vessels by the movements of the body, the contraction of skeletal muscles during body movements, and breathing. One-way valves (semi-lunar valves) in lymphatic vessels keep the lymph moving toward the heart. Lymph flows from the lymphatic capillaries, through lymphatic vessels, and then is dumped into the circulatory system via the lymphatic ducts located at the junction of the jugular and subclavian veins in the neck.

Lymphatic Capillaries

Lymphatic capillaries, also called the terminal lymphatics, are vessels where interstitial fluid enters the lymphatic system to become lymph fluid. Located in almost every tissue in the body, these vessels are interlaced among the arterioles and venules of the circulatory system in the soft connective tissues of the body ([\[link\]](#)). Exceptions are the central nervous system, bone marrow, bones, teeth, and the cornea of the eye, which do not contain lymph vessels.

Lymphatic Capillaries

Lymph capillaries in the tissue spaces



Lymphatic capillaries are interlaced with the arterioles and venules of the cardiovascular system. Collagen fibers anchor a lymphatic capillary in the tissue (inset).

Interstitial fluid slips through spaces between the overlapping endothelial cells that compose the lymphatic capillary.

Lymphatic capillaries are formed by a one cell-thick layer of endothelial cells and represent the open end of the system, allowing interstitial fluid to flow into them via overlapping cells (see [\[link\]](#)). When interstitial pressure is low, the endothelial flaps close to prevent “backflow.” As interstitial pressure increases, the spaces between the cells open up, allowing the fluid

to enter. Entry of fluid into lymphatic capillaries is also enabled by the collagen filaments that anchor the capillaries to surrounding structures. As interstitial pressure increases, the filaments pull on the endothelial cell flaps, opening up them even further to allow easy entry of fluid.

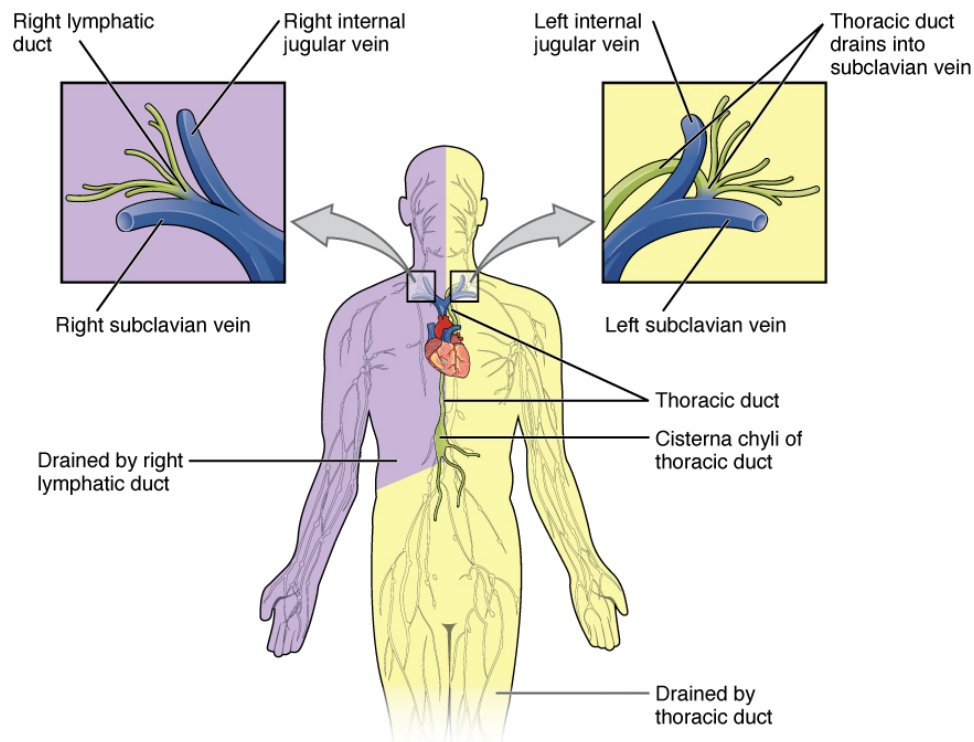
In the small intestine, lymphatic capillaries called lacteals are critical for the transport of dietary lipids and lipid-soluble vitamins to the bloodstream. In the small intestine, dietary triglycerides combine with other lipids and proteins, and enter the lacteals to form a milky fluid called **chyle**. The chyle then travels through the lymphatic system, eventually entering the bloodstream.

Larger Lymphatic Vessels, Trunks, and Ducts

The lymphatic capillaries empty into larger lymphatic vessels, which are similar to veins in terms of their three-tunic structure and the presence of valves. These one-way valves are located fairly close to one another, and each one causes a bulge in the lymphatic vessel, giving the vessels a beaded appearance (see [\[link\]](#)).

The superficial and deep lymphatics eventually merge to form larger lymphatic vessels known as **lymphatic trunks**. On the right side of the body, the right sides of the head, thorax, and right upper limb drain lymph fluid into the right subclavian vein via the right lymphatic duct ([\[link\]](#)). On the left side of the body, the remaining portions of the body drain into the larger thoracic duct, which drains into the left subclavian vein. The thoracic duct itself begins just beneath the diaphragm in the **cisterna chyli**, a sac-like chamber that receives lymph from the lower abdomen, pelvis, and lower limbs by way of the left and right lumbar trunks and the intestinal trunk.

Major Trunks and Ducts of the Lymphatic System



The thoracic duct drains a much larger portion of the body than does the right lymphatic duct.

The overall drainage system of the body is asymmetrical (see [\[link\]](#)). The **right lymphatic duct** receives lymph from only the upper right side of the body. The lymph from the rest of the body enters the bloodstream through the **thoracic duct** via all the remaining lymphatic trunks. In general, lymphatic vessels of the subcutaneous tissues of the skin, that is, the superficial lymphatics, follow the same routes as veins, whereas the deep lymphatic vessels of the viscera generally follow the paths of arteries.

The Organization of Immune Function

The immune system is a collection of barriers, cells, and soluble proteins that interact and communicate with each other in extraordinarily complex ways. The modern model of immune function is organized into three phases

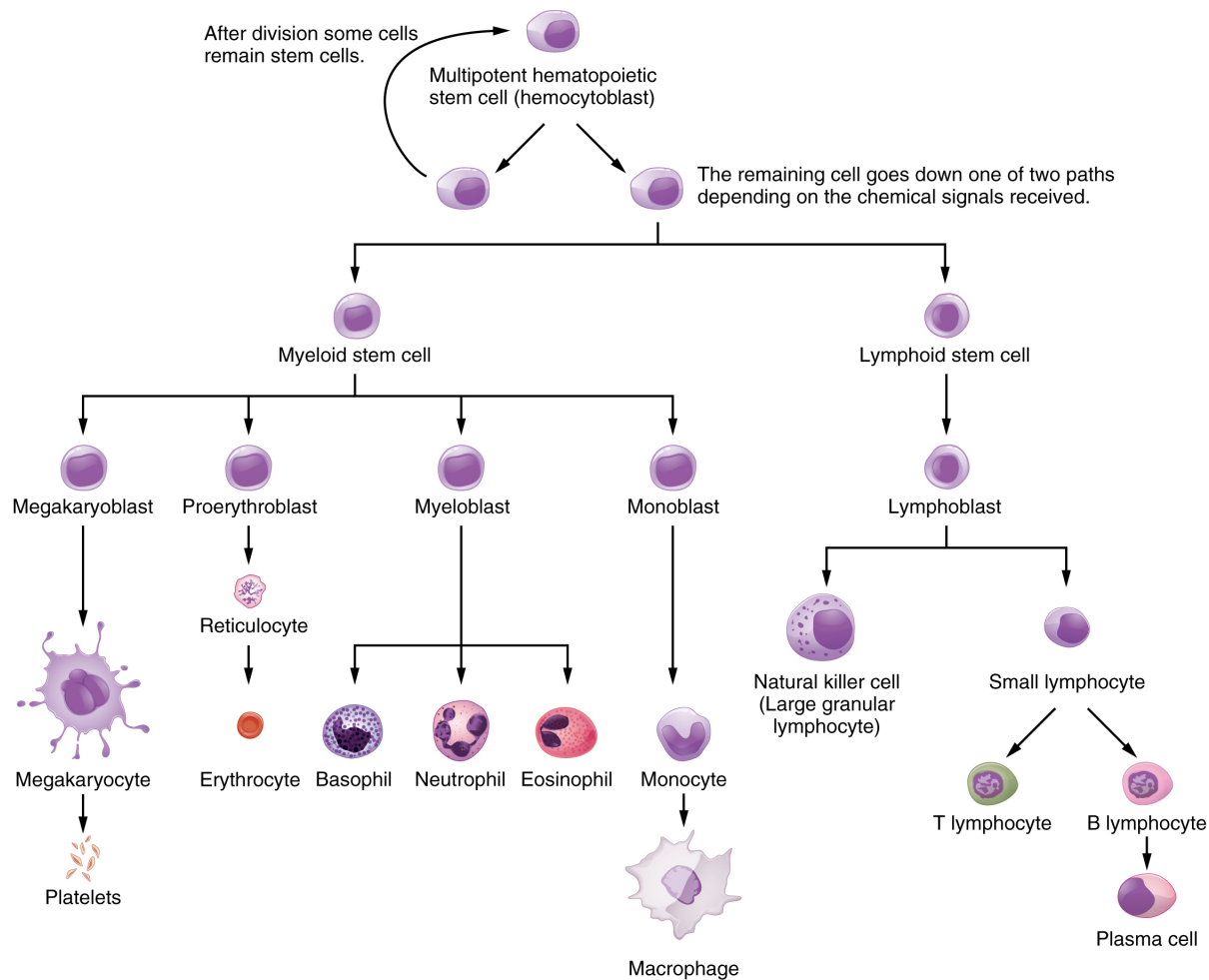
based on the timing of their effects. The three temporal phases consist of the following:

- **Barrier defenses** such as the skin and mucous membranes, which act instantaneously to prevent pathogenic invasion into the body tissues
- The rapid but nonspecific **innate immune response**, which consists of a variety of specialized cells and soluble factors
- The slower but more specific and effective **adaptive immune response**, which involves many cell types and soluble factors, but is primarily controlled by white blood cells (leukocytes) known as **lymphocytes**, which help control immune responses

The cells of the blood, including all those involved in the immune response, arise in the bone marrow via various differentiation pathways from hematopoietic stem cells ([\[link\]](#)). In contrast with embryonic stem cells, hematopoietic stem cells are present throughout adulthood and allow for the continuous differentiation of blood cells to replace those lost to age or function. These cells can be divided into three classes based on function:

- Phagocytic cells, which ingest pathogens to destroy them
- Lymphocytes, which specifically coordinate the activities of adaptive immunity
- Cells containing cytoplasmic granules, which help mediate immune responses against parasites and intracellular pathogens such as viruses

Hematopoietic System of the Bone Marrow



All the cells of the immune response as well as of the blood arise by differentiation from hematopoietic stem cells. Platelets are cell fragments involved in the clotting of blood.

Lymphocytes: B Cells, T Cells, Plasma Cells, and Natural Killer Cells

As stated above, lymphocytes are the primary cells of adaptive immune responses ([\[link\]](#)). The two basic types of lymphocytes, B cells and T cells, are identical morphologically with a large central nucleus surrounded by a thin layer of cytoplasm. They are distinguished from each other by their surface protein markers as well as by the molecules they secrete. While B

cells mature in red bone marrow and T cells mature in the thymus, they both initially develop from bone marrow. T cells migrate from bone marrow to the thymus gland where they further mature. B cells and T cells are found in many parts of the body, circulating in the bloodstream and lymph, and residing in secondary lymphoid organs, including the spleen and lymph nodes, which will be described later in this section. The human body contains approximately 10^{12} lymphocytes.

B Cells

B cells are immune cells that function primarily by producing antibodies. An **antibody** is any of the group of proteins that binds specifically to pathogen-associated molecules known as antigens. An **antigen** is a chemical structure on the surface of a pathogen that binds to T or B lymphocyte antigen receptors. Once activated by binding to antigen, B cells differentiate into cells that secrete a soluble form of their surface antibodies. These activated B cells are known as plasma cells.

T Cells

The **T cell**, on the other hand, does not secrete antibody but performs a variety of functions in the adaptive immune response. Different T cell types have the ability to either secrete soluble factors that communicate with other cells of the adaptive immune response or destroy cells infected with intracellular pathogens. The roles of T and B lymphocytes in the adaptive immune response will be discussed further in this chapter.

Plasma Cells

Another type of lymphocyte of importance is the plasma cell. A **plasma cell** is a B cell that has differentiated in response to antigen binding, and has thereby gained the ability to secrete soluble antibodies. These cells differ in morphology from standard B and T cells in that they contain a large amount

of cytoplasm packed with the protein-synthesizing machinery known as rough endoplasmic reticulum.

Natural Killer Cells

A fourth important lymphocyte is the natural killer cell, a participant in the innate immune response. A **natural killer cell (NK)** is a circulating blood cell that contains cytotoxic (cell-killing) granules in its extensive cytoplasm. It shares this mechanism with the cytotoxic T cells of the adaptive immune response. NK cells are among the body’s first lines of defense against viruses and certain types of cancer.

| Lymphocytes | |
|--------------------|---------------------------------|
| Type of lymphocyte | Primary function |
| B lymphocyte | Generates diverse antibodies |
| T lymphocyte | Secretes chemical messengers |
| Plasma cell | Secretes antibodies |
| NK cell | Destroys virally infected cells |

Note:



Visit this [website](#) to learn about the many different cell types in the immune system and their very specialized jobs. What is the role of the dendritic cell in an HIV infection?

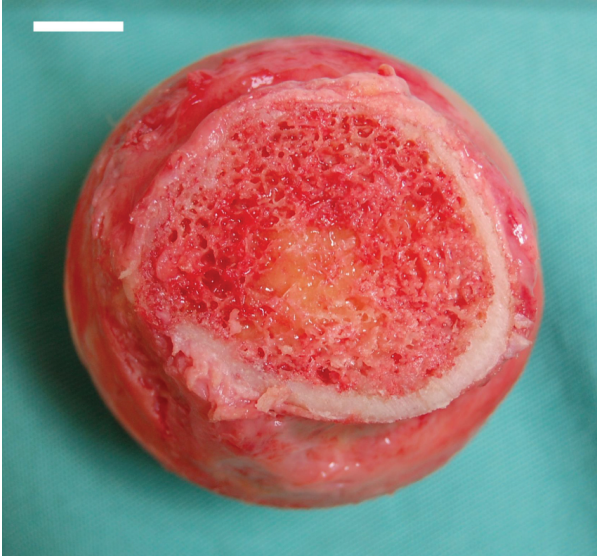
Primary Lymphoid Organs and Lymphocyte Development

Understanding the differentiation and development of B and T cells is critical to the understanding of the adaptive immune response. It is through this process that the body (ideally) learns to destroy only pathogens and leaves the body's own cells relatively intact. The **primary lymphoid organs** are the bone marrow and thymus gland. The lymphoid organs are where lymphocytes mature, proliferate, and are selected, which enables them to attack pathogens without harming the cells of the body.

Bone Marrow

In the embryo, blood cells are made in the yolk sac. As development proceeds, this function is taken over by the spleen, lymph nodes, and liver. Later, the bone marrow takes over most hematopoietic functions, although the final stages of the differentiation of some cells may take place in other organs. The red **bone marrow** is a loose collection of cells where hematopoiesis occurs, and the yellow bone marrow is a site of energy storage, which consists largely of fat cells ([\[link\]](#)). The B cell undergoes nearly all of its development in the red bone marrow, whereas the immature T cell, called a **thymocyte**, leaves the bone marrow and matures largely in the thymus gland.

Bone Marrow

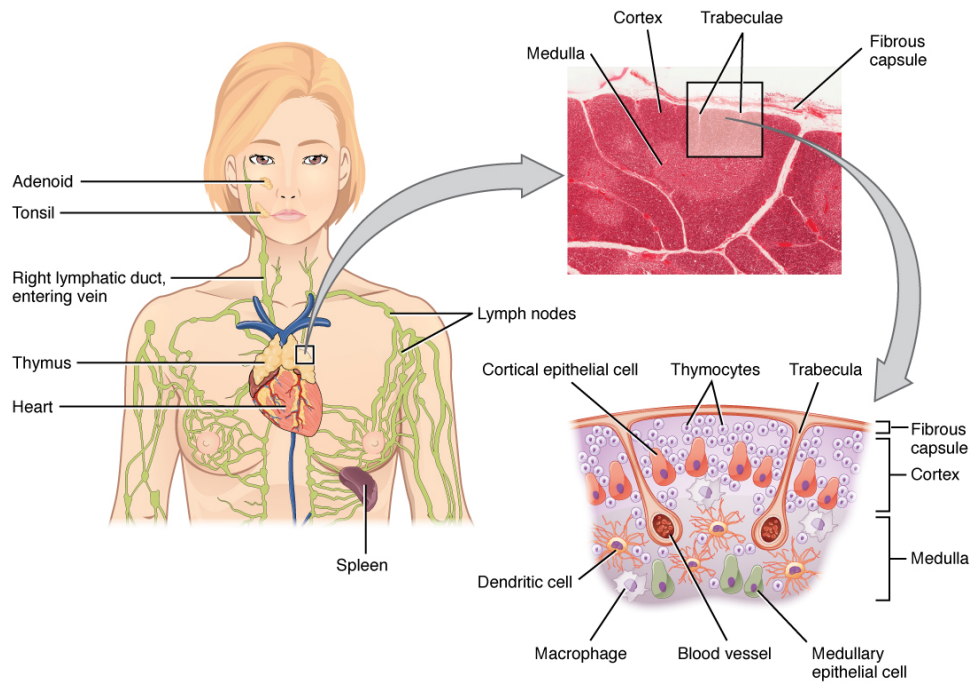


Red bone marrow fills the head of the femur, and a spot of yellow bone marrow is visible in the center. The white reference bar is 1 cm.

Thymus

The **thymus** gland is a bilobed organ found in the space between the sternum and the aorta of the heart ([\[link\]](#)). Connective tissue holds the lobes closely together but also separates them and forms a capsule.

Location, Structure, and Histology of the Thymus



The thymus lies above the heart. The trabeculae and lobules, including the darkly staining cortex and the lighter staining medulla of each lobule, are clearly visible in the light micrograph of the thymus of a newborn. LM $\times 100$. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Note:



View the [University of Michigan WebScope](#) to explore the tissue sample in greater detail.

The connective tissue capsule further divides the thymus into lobules via extensions called trabeculae. The outer region of the organ is known as the cortex and contains large numbers of thymocytes with some epithelial cells, macrophages, and dendritic cells (two types of phagocytic cells that are derived from monocytes). The cortex is densely packed so it stains more intensely than the rest of the thymus (see [\[link\]](#)). The medulla, where thymocytes migrate before leaving the thymus, contains a less dense collection of thymocytes, epithelial cells, and dendritic cells.

Note:

Aging and the...

Immune System

By the year 2050, 25 percent of the population of the United States will be 60 years of age or older. The CDC estimates that 80 percent of those 60 years and older have one or more chronic disease associated with deficiencies of the immune systems. This loss of immune function with age is called immunosenescence. To treat this growing population, medical professionals must better understand the aging process. One major cause of age-related immune deficiencies is thymic involution, the shrinking of the thymus gland that begins at birth, at a rate of about three percent tissue loss per year, and continues until 35–45 years of age, when the rate declines to about one percent loss per year for the rest of one's life. At that pace, the total loss of thymic epithelial tissue and thymocytes would occur at about 120 years of age. Thus, this age is a theoretical limit to a healthy human lifespan.

Thymic involution has been observed in all vertebrate species that have a thymus gland. Animal studies have shown that transplanted thymic grafts between inbred strains of mice involuted according to the age of the donor and not of the recipient, implying the process is genetically programmed. There is evidence that the thymic microenvironment, so vital to the

development of naïve T cells, loses thymic epithelial cells according to the decreasing expression of the FOXP1 gene with age.

It is also known that thymic involution can be altered by hormone levels. Sex hormones such as estrogen and testosterone enhance involution, and the hormonal changes in pregnant women cause a temporary thymic involution that reverses itself, when the size of the thymus and its hormone levels return to normal, usually after lactation ceases. What does all this tell us? Can we reverse immunosenescence, or at least slow it down? The potential is there for using thymic transplants from younger donors to keep thymic output of naïve T cells high. Gene therapies that target gene expression are also seen as future possibilities. The more we learn through immunosenescence research, the more opportunities there will be to develop therapies, even though these therapies will likely take decades to develop. The ultimate goal is for everyone to live and be healthy longer, but there may be limits to immortality imposed by our genes and hormones.

Secondary Lymphoid Organs and their Roles in Active Immune Responses

Lymphocytes develop and mature in the primary lymphoid organs, but they mount immune responses from the **secondary lymphoid organs**. A **naïve lymphocyte** is one that has left the primary organ and entered a secondary lymphoid organ. Naïve lymphocytes are fully functional immunologically, but have yet to encounter an antigen to respond to. In addition to circulating in the blood and lymph, lymphocytes concentrate in secondary lymphoid organs, which include the lymph nodes, spleen, and lymphoid nodules. All of these tissues have many features in common, including the following:

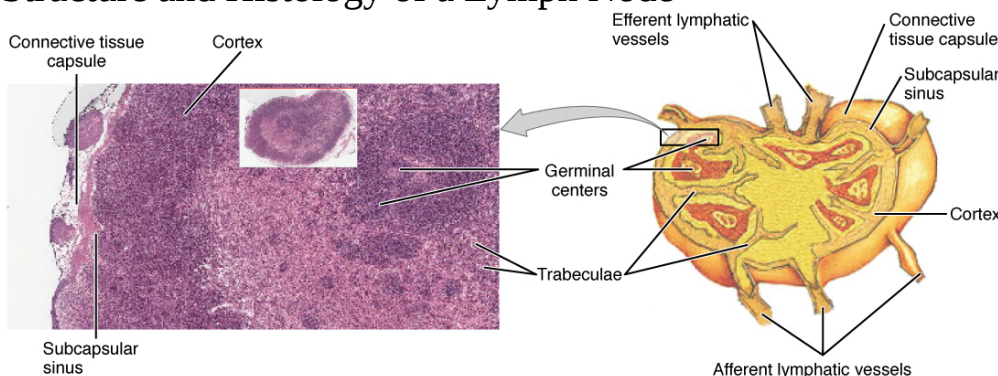
- The presence of lymphoid follicles, the sites of the formation of lymphocytes, with specific B cell-rich and T cell-rich areas
- An internal structure of reticular fibers with associated fixed macrophages
- **Germinal centers**, which are the sites of rapidly dividing and differentiating B lymphocytes

- Specialized post-capillary vessels known as **high endothelial venules**; the cells lining these venules are thicker and more columnar than normal endothelial cells, which allow cells from the blood to directly enter these tissues

Lymph Nodes

Lymph nodes function to remove debris and pathogens from the lymph, and are thus sometimes referred to as the “filters of the lymph” ([\[link\]](#)). Any bacteria that infect the interstitial fluid are taken up by the lymphatic capillaries and transported to a regional lymph node. Dendritic cells and macrophages within this organ internalize and kill many of the pathogens that pass through, thereby removing them from the body. The lymph node is also the site of adaptive immune responses mediated by T cells, B cells, and accessory cells of the adaptive immune system. Like the thymus, the bean-shaped lymph nodes are surrounded by a tough capsule of connective tissue and are separated into compartments by trabeculae, the extensions of the capsule. In addition to the structure provided by the capsule and trabeculae, the structural support of the lymph node is provided by a series of reticular fibers laid down by fibroblasts.

Structure and Histology of a Lymph Node



Lymph nodes are masses of lymphatic tissue located along the larger lymph vessels. The micrograph of the lymph nodes shows a germinal center, which consists of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. LM $\times 128$. (Micrograph

provided by the Regents of the University of Michigan
Medical School © 2012)

Note:



View the [University of Michigan WebScope](#) to explore the tissue sample in greater detail.

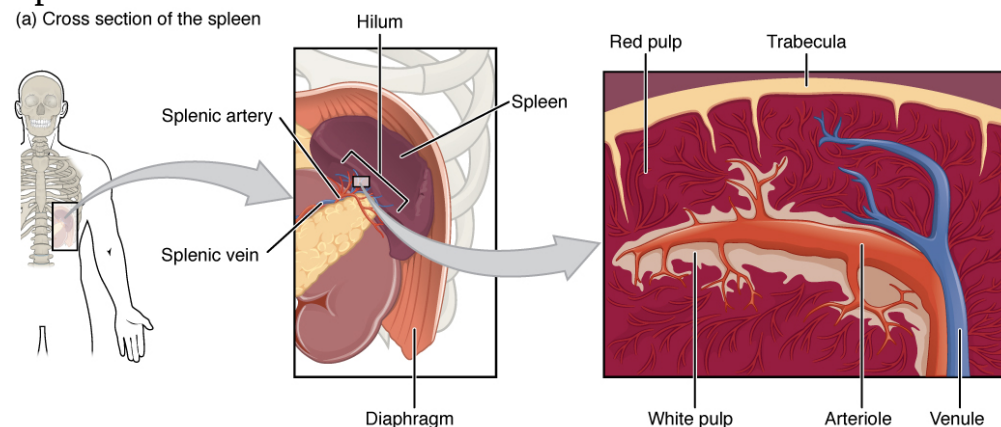
The major routes into the lymph node are via **afferent lymphatic vessels** (see [\[link\]](#)). Cells and lymph fluid that leave the lymph node may do so by another set of vessels known as the **efferent lymphatic vessels**. Lymph enters the lymph node via the subcapsular sinus, which is occupied by dendritic cells, macrophages, and reticular fibers. Within the cortex of the lymph node are lymphoid follicles, which consist of germinal centers of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. As the lymph continues to flow through the node, it enters the medulla, which consists of medullary cords of B cells and plasma cells, and the medullary sinuses where the lymph collects before leaving the node via the efferent lymphatic vessels.

Spleen

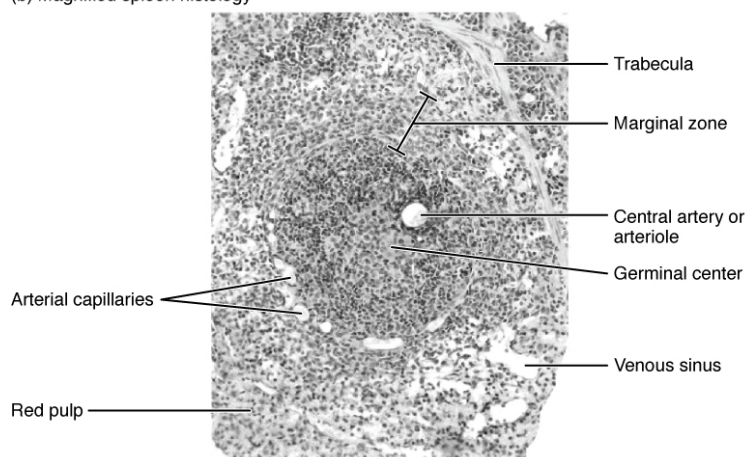
In addition to the lymph nodes, the **spleen** is a major secondary lymphoid organ ([\[link\]](#)). It is about 12 cm (5 in) long and is attached to the lateral

border of the stomach via the gastrosplenic ligament. The spleen is a fragile organ without a strong capsule, and is dark red due to its extensive vascularization. The spleen is sometimes called the “filter of the blood” because of its extensive vascularization and the presence of macrophages and dendritic cells that remove microbes and other materials from the blood, including dying red blood cells. The spleen also functions as the location of immune responses to blood-borne pathogens.

Spleen



(b) Magnified spleen histology



(a) The spleen is attached to the stomach. (b) A micrograph of spleen tissue shows the germinal center. The marginal zone is the region between the red pulp and white pulp, which sequesters particulate antigens from the circulation and presents these antigens to lymphocytes in the white pulp. EM $\times 660$. (Micrograph

provided by the Regents of the University of Michigan
Medical School © 2012)

The spleen is also divided by trabeculae of connective tissue, and within each splenic nodule is an area of red pulp, consisting of mostly red blood cells, and white pulp, which resembles the lymphoid follicles of the lymph nodes. Upon entering the spleen, the splenic artery splits into several arterioles (surrounded by white pulp) and eventually into sinusoids. Blood from the capillaries subsequently collects in the venous sinuses and leaves via the splenic vein. The red pulp consists of reticular fibers with fixed macrophages attached, free macrophages, and all of the other cells typical of the blood, including some lymphocytes. The white pulp surrounds a central arteriole and consists of germinal centers of dividing B cells surrounded by T cells and accessory cells, including macrophages and dendritic cells. Thus, the red pulp primarily functions as a filtration system of the blood, using cells of the relatively nonspecific immune response, and white pulp is where adaptive T and B cell responses are mounted.

Lymphoid Nodules

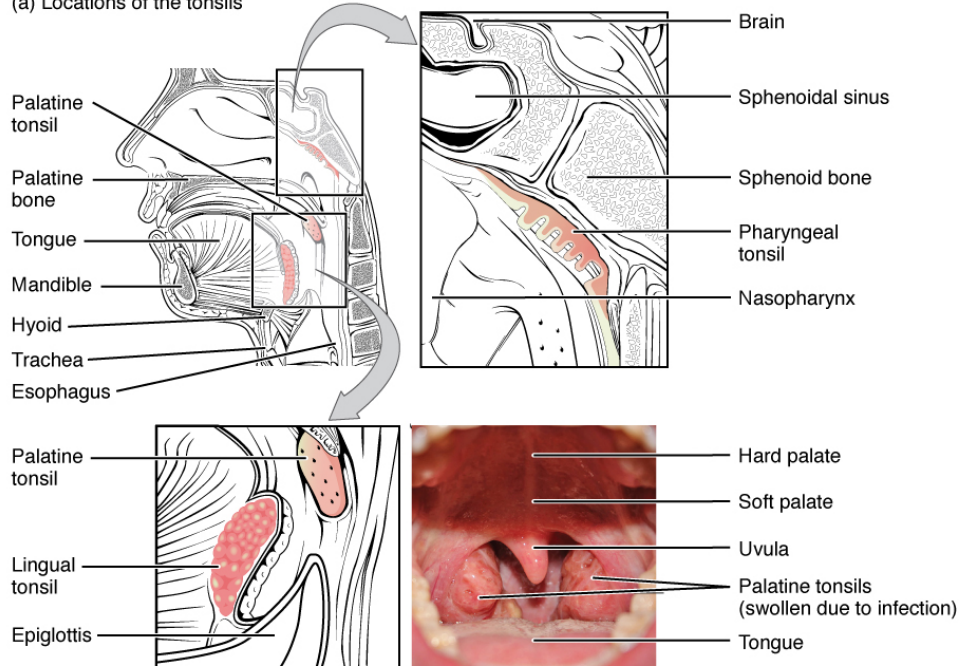
The other lymphoid tissues, the **lymphoid nodules**, have a simpler architecture than the spleen and lymph nodes in that they consist of a dense cluster of lymphocytes without a surrounding fibrous capsule. These nodules are located in the respiratory and digestive tracts, areas routinely exposed to environmental pathogens.

Tonsils are lymphoid nodules located along the inner surface of the pharynx and are important in developing immunity to oral pathogens ([\[link\]](#)). The tonsil located at the back of the throat, the pharyngeal tonsil, is sometimes referred to as the adenoid when swollen. Such swelling is an indication of an active immune response to infection. Histologically, tonsils do not contain a complete capsule, and the epithelial layer invaginates deeply into the interior of the tonsil to form tonsillar crypts. These structures, which accumulate all sorts of materials taken into the body through eating and breathing, actually “encourage” pathogens to penetrate deep into the

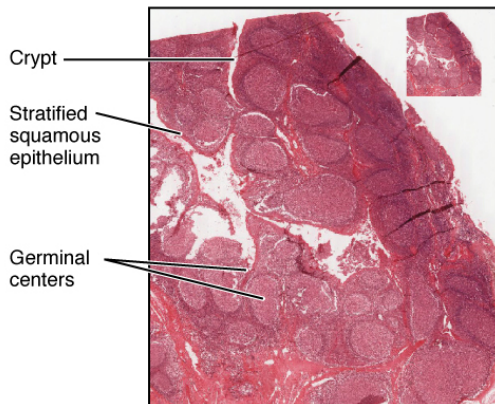
tonsillar tissues where they are acted upon by numerous lymphoid follicles and eliminated. This seems to be the major function of tonsils—to help children's bodies recognize, destroy, and develop immunity to common environmental pathogens so that they will be protected in their later lives. Tonsils are often removed in those children who have recurring throat infections, especially those involving the palatine tonsils on either side of the throat, whose swelling may interfere with their breathing and/or swallowing.

Locations and Histology of the Tonsils

(a) Locations of the tonsils



(b) Histology of palatine tonsil



(a) The pharyngeal tonsil is located on the roof of the posterior superior wall of the nasopharynx. The palatine tonsils lay on each side of the pharynx. (b) A micrograph shows the palatine tonsil tissue. LM \times 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Note:



View the [University of Michigan WebScope](#) to explore the tissue sample in greater detail.

Mucosa-associated lymphoid tissue (MALT) consists of an aggregate of lymphoid follicles directly associated with the mucous membrane epithelia. MALT makes up dome-shaped structures found underlying the mucosa of the gastrointestinal tract, breast tissue, lungs, and eyes. Peyer's patches, a type of MALT in the small intestine, are especially important for immune responses against ingested substances ([link](#)). Peyer's patches contain specialized endothelial cells called M (or microfold) cells that sample material from the intestinal lumen and transport it to nearby follicles so that adaptive immune responses to potential pathogens can be mounted.

Mucosa-associated Lymphoid Tissue (MALT) Nodule



LM \times 40. (Micrograph provided by the Regents of the University of Michigan Medical School \copyright 2012)

Bronchus-associated lymphoid tissue (BALT) consists of lymphoid follicular structures with an overlying epithelial layer found along the bifurcations of the bronchi, and between bronchi and arteries. They also have the typically less-organized structure of other lymphoid nodules. These tissues, in addition to the tonsils, are effective against inhaled pathogens.

Chapter Review

The lymphatic system is a series of vessels, ducts, and trunks that remove interstitial fluid from the tissues and return it to the blood. The lymphatics are also used to transport dietary lipids and cells of the immune system. Cells of the immune system all come from the hematopoietic system of the bone marrow. Primary lymphoid organs, the bone marrow and thymus gland, are the locations where lymphocytes of the adaptive immune system proliferate and mature. Secondary lymphoid organs are sites in which mature

lymphocytes congregate to mount immune responses. Many immune system cells use the lymphatic and circulatory systems for transport throughout the body to search for and then protect against pathogens.

Interactive Link Questions

Exercise:

Problem:

Visit this [website](#) for an overview of the lymphatic system. What are the three main components of the lymphatic system?

Solution:

The three main components are the lymph vessels, the lymph nodes, and the lymph.

Exercise:

Problem:

Visit this [website](#) to learn about the many different cell types in the immune system and their very specialized jobs. What is the role of the dendritic cell in infection by HIV?

Solution:

The dendritic cell transports the virus to a lymph node.

Review Questions

Exercise:

Problem: Which of the following cells is phagocytic?

- a. plasma cell
- b. macrophage

- c. B cell
- d. NK cell

Solution:

B

Exercise:

Problem:

Which structure allows lymph from the lower right limb to enter the bloodstream?

- a. thoracic duct
- b. right lymphatic duct
- c. right lymphatic trunk
- d. left lymphatic trunk

Solution:

A

Exercise:

Problem:

Which of the following cells is important in the innate immune response?

- a. B cells
- b. T cells
- c. macrophages
- d. plasma cells

Solution:

C

Exercise:

Problem:

Which of the following cells would be most active in early, antiviral immune responses the first time one is exposed to pathogen?

- a. macrophage
- b. T cell
- c. neutrophil
- d. natural killer cell

Solution:

D

Exercise:

Problem:

Which of the lymphoid nodules is most likely to see food antigens first?

- a. tonsils
- b. Peyer's patches
- c. bronchus-associated lymphoid tissue
- d. mucosa-associated lymphoid tissue

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

Describe the flow of lymph from its origins in interstitial fluid to its emptying into the venous bloodstream.

Solution:

The lymph enters through lymphatic capillaries, and then into larger lymphatic vessels. The lymph can only go in one direction due to valves in the vessels. The larger lymphatics merge to form trunks that enter into the blood via lymphatic ducts.

Glossary

adaptive immune response

relatively slow but very specific and effective immune response
controlled by lymphocytes

afferent lymphatic vessels

lead into a lymph node

antibody

antigen-specific protein secreted by plasma cells; immunoglobulin

antigen

molecule recognized by the receptors of B and T lymphocytes

barrier defenses

antipathogen defenses deriving from a barrier that physically prevents
pathogens from entering the body to establish an infection

B cells

lymphocytes that act by differentiating into an antibody-secreting
plasma cell

bone marrow

tissue found inside bones; the site of all blood cell differentiation and maturation of B lymphocytes

bronchus-associated lymphoid tissue (BALT)

lymphoid nodule associated with the respiratory tract

chyle

lipid-rich lymph inside the lymphatic capillaries of the small intestine

cisterna chyli

bag-like vessel that forms the beginning of the thoracic duct

efferent lymphatic vessels

lead out of a lymph node

germinal centers

clusters of rapidly proliferating B cells found in secondary lymphoid tissues

high endothelial venules

vessels containing unique endothelial cells specialized to allow migration of lymphocytes from the blood to the lymph node

immune system

series of barriers, cells, and soluble mediators that combine to response to infections of the body with pathogenic organisms

innate immune response

rapid but relatively nonspecific immune response

lymph

fluid contained within the lymphatic system

lymph node

one of the bean-shaped organs found associated with the lymphatic vessels

lymphatic capillaries

smallest of the lymphatic vessels and the origin of lymph flow

lymphatic system

network of lymphatic vessels, lymph nodes, and ducts that carries lymph from the tissues and back to the bloodstream.

lymphatic trunks

large lymphatics that collect lymph from smaller lymphatic vessels and empties into the blood via lymphatic ducts

lymphocytes

white blood cells characterized by a large nucleus and small rim of cytoplasm

lymphoid nodules

unencapsulated patches of lymphoid tissue found throughout the body

mucosa-associated lymphoid tissue (MALT)

lymphoid nodule associated with the mucosa

naïve lymphocyte

mature B or T cell that has not yet encountered antigen for the first time

natural killer cell (NK)

cytotoxic lymphocyte of innate immune response

plasma cell

differentiated B cell that is actively secreting antibody

primary lymphoid organ

site where lymphocytes mature and proliferate; red bone marrow and thymus gland

right lymphatic duct

drains lymph fluid from the upper right side of body into the right subclavian vein

secondary lymphoid organs

sites where lymphocytes mount adaptive immune responses; examples include lymph nodes and spleen

spleen

secondary lymphoid organ that filters pathogens from the blood (white pulp) and removes degenerating or damaged blood cells (red pulp)

T cell

lymphocyte that acts by secreting molecules that regulate the immune system or by causing the destruction of foreign cells, viruses, and cancer cells

thoracic duct

large duct that drains lymph from the lower limbs, left thorax, left upper limb, and the left side of the head

thymocyte

immature T cell found in the thymus

thymus

primary lymphoid organ; where T lymphocytes proliferate and mature

tonsils

lymphoid nodules associated with the nasopharynx

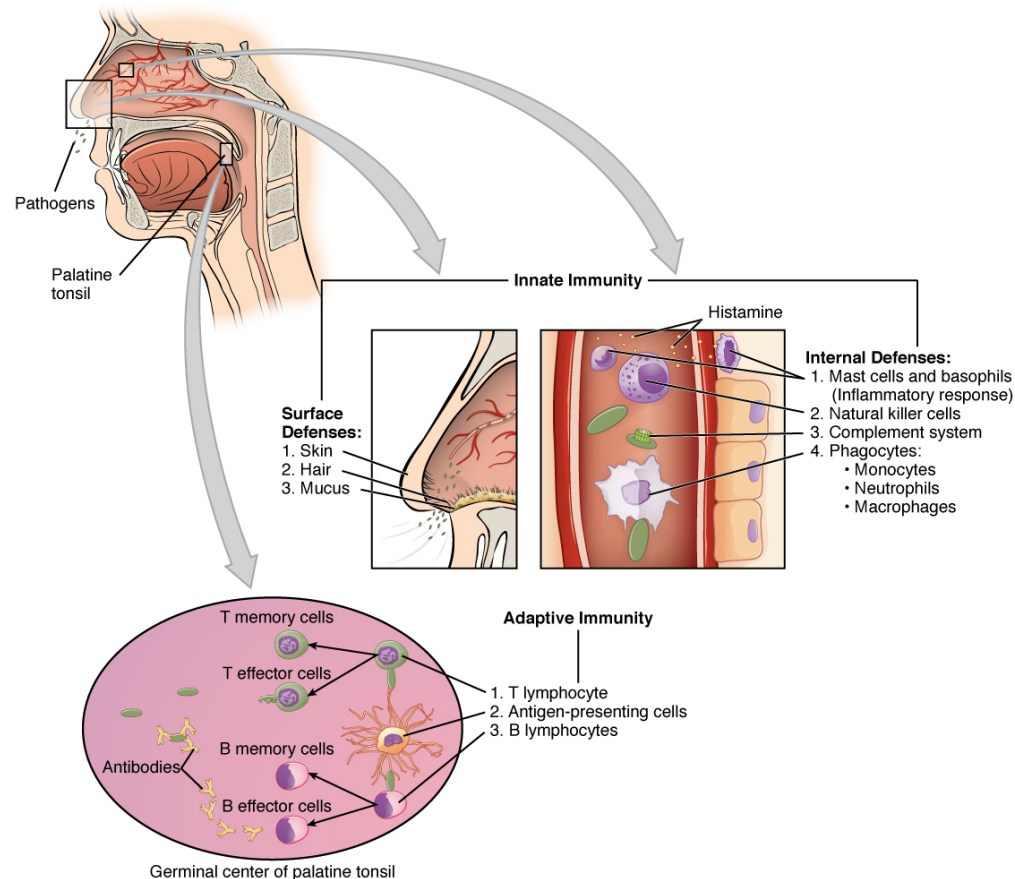
Barrier Defenses and the Innate Immune Response

By the end of this section, you will be able to:

- Describe the barrier defenses of the body
- Show how the innate immune response is important and how it helps guide and prepare the body for adaptive immune responses
- Describe various soluble factors that are part of the innate immune response
- Explain the steps of inflammation and how they lead to destruction of a pathogen
- Discuss early induced immune responses and their level of effectiveness

The immune system can be divided into two overlapping mechanisms to destroy pathogens: the innate immune response, which is relatively rapid but nonspecific and thus not always effective, and the adaptive immune response, which is slower in its development during an initial infection with a pathogen, but is highly specific and effective at attacking a wide variety of pathogens ([link](#)).

Cooperation between Innate and Adaptive Immune Responses



The innate immune system enhances adaptive immune responses so they can be more effective.

Any discussion of the innate immune response usually begins with the physical barriers that prevent pathogens from entering the body, destroy them after they enter, or flush them out before they can establish themselves in the hospitable environment of the body’s soft tissues. Barrier defenses are part of the body’s most basic defense mechanisms. The barrier defenses are not a response to infections, but they are continuously working to protect against a broad range of pathogens.

The different modes of barrier defenses are associated with the external surfaces of the body, where pathogens may try to enter ([link](#)). The primary barrier to the entrance of microorganisms into the body is the skin. Not only is the skin covered with a layer of dead, keratinized epithelium that is too dry for bacteria in which to grow, but as these cells are continuously sloughed off from the skin, they carry bacteria and other pathogens with them. Additionally, sweat and other skin secretions may lower pH, contain toxic lipids, and physically wash microbes away.

| Barrier Defenses | | |
|-------------------------|--------------------------------|--|
| Site | Specific defense | Protective aspect |
| Skin | Epidermal surface | Keratinized cells of surface, Langerhans cells |
| Skin (sweat/secretions) | Sweat glands, sebaceous glands | Low pH, washing action |
| Oral cavity | Salivary glands | Lysozyme |
| Stomach | Gastrointestinal tract | Low pH |

| Barrier Defenses | | |
|---------------------------------------|--------------------|--|
| Site | Specific defense | Protective aspect |
| Mucosal surfaces | Mucosal epithelium | Nonkeratinized epithelial cells |
| Normal flora (nonpathogenic bacteria) | Mucosal tissues | Prevent pathogens from growing on mucosal surfaces |

Another barrier is the saliva in the mouth, which is rich in lysozyme—an enzyme that destroys bacteria by digesting their cell walls. The acidic environment of the stomach, which is fatal to many pathogens, is also a barrier. Additionally, the mucus layer of the gastrointestinal tract, respiratory tract, reproductive tract, eyes, ears, and nose traps both microbes and debris, and facilitates their removal. In the case of the upper respiratory tract, ciliated epithelial cells move potentially contaminated mucus upwards to the mouth, where it is then swallowed into the digestive tract, ending up in the harsh acidic environment of the stomach. Considering how often you breathe compared to how often you eat or perform other activities that expose you to pathogens, it is not surprising that multiple barrier mechanisms have evolved to work in concert to protect this vital area.

Cells of the Innate Immune Response

A phagocyte is a cell that is able to surround and engulf a particle or cell, a process called **phagocytosis**. The phagocytes of the immune system engulf other particles or cells, either to clean an area of debris, old cells, or to kill pathogenic organisms such as bacteria. The phagocytes are the body's fast acting, first line of immunological defense against organisms that have breached barrier defenses and have entered the vulnerable tissues of the body.

Phagocytes: Macrophages and Neutrophils

Many of the cells of the immune system have a phagocytic ability, at least at some point during their life cycles. Phagocytosis is an important and effective mechanism of destroying pathogens during innate immune responses. The phagocyte takes the

organism inside itself as a phagosome, which subsequently fuses with a lysosome and its digestive enzymes, effectively killing many pathogens. On the other hand, some bacteria including *Mycobacteria tuberculosis*, the cause of tuberculosis, may be resistant to these enzymes and are therefore much more difficult to clear from the body. Macrophages, neutrophils, and dendritic cells are the major phagocytes of the immune system.

A **macrophage** is an irregularly shaped phagocyte that is amoeboid in nature and is the most versatile of the phagocytes in the body. Macrophages move through tissues and squeeze through capillary walls using pseudopodia. They not only participate in innate immune responses but have also evolved to cooperate with lymphocytes as part of the adaptive immune response. Macrophages exist in many tissues of the body, either freely roaming through connective tissues or fixed to reticular fibers within specific tissues such as lymph nodes. When pathogens breach the body's barrier defenses, macrophages are the first line of defense ([\[link\]](#)). They are called different names, depending on the tissue: Kupffer cells in the liver, histiocytes in connective tissue, and alveolar macrophages in the lungs.

A **neutrophil** is a phagocytic cell that is attracted via chemotaxis from the bloodstream to infected tissues. These spherical cells are granulocytes. A granulocyte contains cytoplasmic granules, which in turn contain a variety of vasoactive mediators such as histamine. In contrast, macrophages are agranulocytes. An agranulocyte has few or no cytoplasmic granules. Whereas macrophages act like sentries, always on guard against infection, neutrophils can be thought of as military reinforcements that are called into a battle to hasten the destruction of the enemy. Although, usually thought of as the primary pathogen-killing cell of the inflammatory process of the innate immune response, new research has suggested that neutrophils play a role in the adaptive immune response as well, just as macrophages do.

A **monocyte** is a circulating precursor cell that differentiates into either a macrophage or dendritic cell, which can be rapidly attracted to areas of infection by signal molecules of inflammation.

Phagocytic Cells of the Innate Immune System

| Phagocytic Cells of the Innate Immune System | | | Function in the innate immune response |
|--|--------------|----------------------|--|
| Cell | Cell type | Primary location | |
| Macrophage | Agranulocyte | Body cavities/organs | Phagocytosis |
| Neutrophil | Granulocyte | Blood | Phagocytosis |
| Monocyte | Agranulocyte | Blood | Precursor of macrophage/dendritic cell |

Natural Killer Cells

NK cells are a type of lymphocyte that have the ability to induce apoptosis, that is, programmed cell death, in cells infected with intracellular pathogens such as obligate intracellular bacteria and viruses. NK cells recognize these cells by mechanisms that are still not well understood, but that presumably involve their surface receptors. NK cells can induce apoptosis, in which a cascade of events inside the cell causes its own death by either of two mechanisms:

1) NK cells are able to respond to chemical signals and express the fas ligand. The **fas ligand** is a surface molecule that binds to the fas molecule on the surface of the infected cell, sending it apoptotic signals, thus killing the cell and the pathogen within it; or

2) The granules of the NK cells release perforins and granzymes. A **perforin** is a protein that forms pores in the membranes of infected cells. A **granzyme** is a protein-digesting enzyme that enters the cell via the perforin pores and triggers apoptosis intracellularly.

Both mechanisms are especially effective against virally infected cells. If apoptosis is induced before the virus has the ability to synthesize and assemble all its components, no infectious virus will be released from the cell, thus preventing further infection.

Recognition of Pathogens

Cells of the innate immune response, the phagocytic cells, and the cytotoxic NK cells recognize patterns of pathogen-specific molecules, such as bacterial cell wall components or bacterial flagellar proteins, using pattern recognition receptors. A **pattern recognition receptor (PRR)** is a membrane-bound receptor that recognizes characteristic features of a pathogen and molecules released by stressed or damaged cells.

These receptors, which are thought to have evolved prior to the adaptive immune response, are present on the cell surface whether they are needed or not. Their variety, however, is limited by two factors. First, the fact that each receptor type must be encoded by a specific gene requires the cell to allocate most or all of its DNA to make receptors able to recognize all pathogens. Secondly, the variety of receptors is limited by the finite surface area of the cell membrane. Thus, the innate immune system must “get by” using only a limited number of receptors that are active against as wide a variety of pathogens as possible. This strategy is in stark contrast to the approach used by the adaptive immune system, which uses large numbers of different receptors, each highly specific to a particular pathogen.

Should the cells of the innate immune system come into contact with a species of pathogen they recognize, the cell will bind to the pathogen and initiate phagocytosis (or cellular apoptosis in the case of an intracellular pathogen) in an effort to destroy the offending microbe. Receptors vary somewhat according to cell type, but they usually include receptors for bacterial components and for complement, discussed below.

Soluble Mediators of the Innate Immune Response

The previous discussions have alluded to chemical signals that can induce cells to change various physiological characteristics, such as the expression of a particular receptor. These soluble factors are secreted during innate or early induced responses, and later during adaptive immune responses.

Cytokines and Chemokines

A **cytokine** is signaling molecule that allows cells to communicate with each other over short distances. Cytokines are secreted into the intercellular space, and the action of the cytokine induces the receiving cell to change its physiology. A **chemokine** is a soluble chemical mediator similar to cytokines except that its function is to attract cells (chemotaxis) from longer distances.

Note:



Visit this [website](#) to learn about phagocyte chemotaxis. Phagocyte chemotaxis is the movement of phagocytes according to the secretion of chemical messengers in the form of interleukins and other chemokines. By what means does a phagocyte destroy a bacterium that it has ingested?

Early induced Proteins

Early induced proteins are those that are not constitutively present in the body, but are made as they are needed early during the innate immune response. **Interferons** are an example of early induced proteins. Cells infected with viruses secrete interferons that travel to adjacent cells and induce them to make antiviral proteins. Thus, even though the initial cell is sacrificed, the surrounding cells are protected. Other early induced proteins specific for bacterial cell wall components are mannose-binding protein and C-reactive protein, made in the liver, which bind specifically to polysaccharide components of the bacterial cell wall. Phagocytes such as macrophages have receptors for these proteins, and they are thus able to recognize them as they are bound to the bacteria. This brings the phagocyte and bacterium into close proximity and enhances the phagocytosis of the bacterium by the process known as opsonization. **Opsonization** is the tagging of a pathogen for phagocytosis by the binding of an antibody or an antimicrobial protein.

Complement System

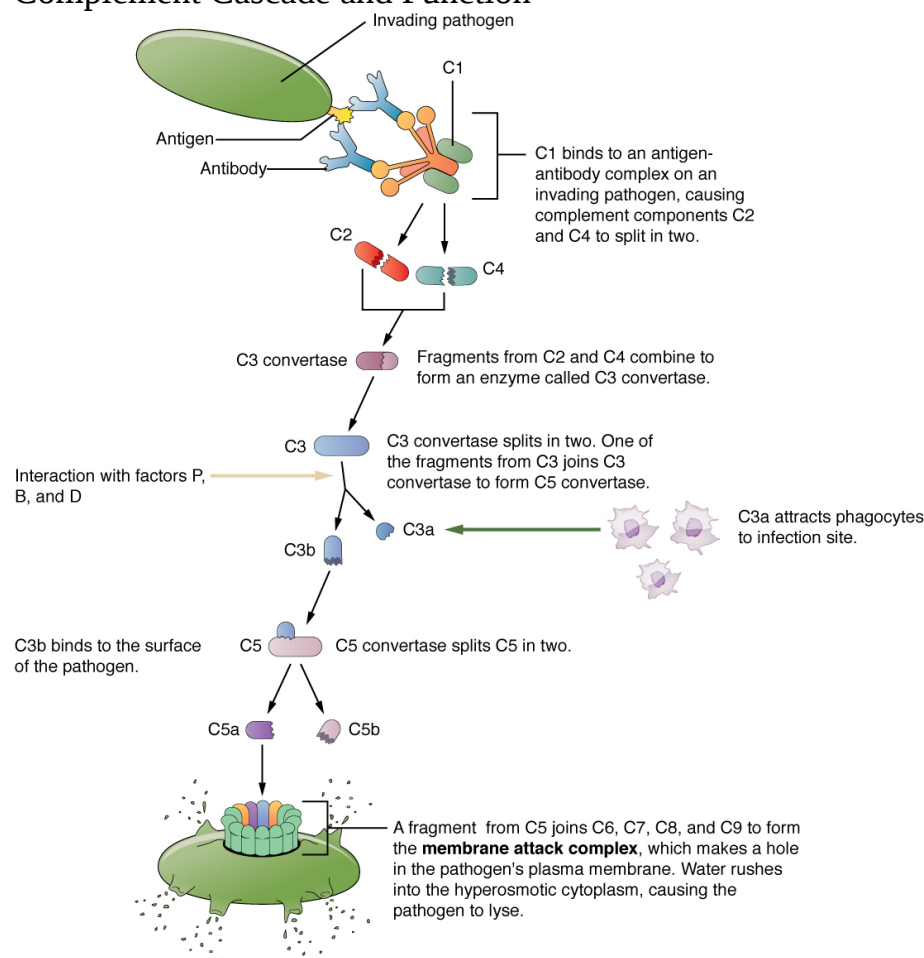
The **complement** system is a series of proteins constitutively found in the blood plasma. As such, these proteins are not considered part of the **early induced immune response**, even though they share features with some of the antibacterial proteins of this class. Made in the liver, they have a variety of functions in the innate immune response, using what is known as the “alternate pathway” of complement activation. Additionally, complement functions in the adaptive immune response as well, in what is called the classical pathway. The complement

system consists of several proteins that enzymatically alter and fragment later proteins in a series, which is why it is termed cascade. Once activated, the series of reactions is irreversible, and releases fragments that have the following actions:

- Bind to the cell membrane of the pathogen that activates it, labeling it for phagocytosis (opsonization)
- Diffuse away from the pathogen and act as chemotactic agents to attract phagocytic cells to the site of inflammation
- Form damaging pores in the plasma membrane of the pathogen

[\[link\]](#) shows the classical pathway, which requires antibodies of the adaptive immune response. The alternate pathway does not require an antibody to become activated.

Complement Cascade and Function

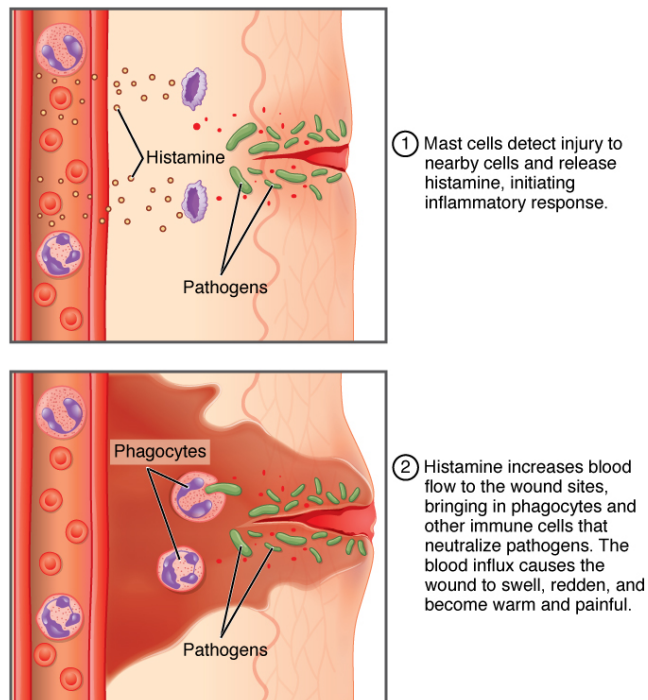


The classical pathway, used during adaptive immune responses, occurs when C1 reacts with antibodies that have bound an antigen.

The splitting of the C3 protein is the common step to both pathways. In the alternate pathway, C3 is activated spontaneously and, after reacting with the molecules factor P, factor B, and factor D, splits apart. The larger fragment, C3b, binds to the surface of the pathogen and C3a, the smaller fragment, diffuses outward from the site of activation and attracts phagocytes to the site of infection. Surface-bound C3b then activates the rest of the cascade, with the last five proteins, C5–C9, forming the membrane-attack complex (MAC). The MAC can kill certain pathogens by disrupting their osmotic balance. The MAC is especially effective against a broad range of bacteria. The classical pathway is similar, except the early stages of activation require the presence of antibody bound to antigen, and thus is dependent on the adaptive immune response. The earlier fragments of the cascade also have important functions. Phagocytic cells such as macrophages and neutrophils are attracted to an infection site by chemotactic attraction to smaller complement fragments. Additionally, once they arrive, their receptors for surface-bound C3b opsonize the pathogen for phagocytosis and destruction.

Inflammatory Response

The hallmark of the innate immune response is **inflammation**. Inflammation is something everyone has experienced. Stub a toe, cut a finger, or do any activity that causes tissue damage and inflammation will result, with its four characteristics: heat, redness, pain, and swelling (“loss of function” is sometimes mentioned as a fifth characteristic). It is important to note that inflammation does not have to be initiated by an infection, but can also be caused by tissue injuries. The release of damaged cellular contents into the site of injury is enough to stimulate the response, even in the absence of breaks in physical barriers that would allow pathogens to enter (by hitting your thumb with a hammer, for example). The inflammatory reaction brings in phagocytic cells to the damaged area to clear cellular debris and to set the stage for wound repair ([\[link\]](#)).



This reaction also brings in the cells of the innate immune system, allowing them to get rid of the sources of a possible infection. Inflammation is part of a very basic form of immune response. The process not only brings fluid and cells into the site to destroy the pathogen and remove it and debris from the site, but also helps to isolate the site, limiting the spread of the pathogen. **Acute inflammation** is a short-term inflammatory response to an insult to the body. If the cause of the inflammation is not resolved, however, it can lead to chronic inflammation, which is associated with major tissue destruction and fibrosis. **Chronic inflammation** is ongoing inflammation. It can be caused by foreign bodies, persistent pathogens, and autoimmune diseases such as rheumatoid arthritis.

There are four important parts to the inflammatory response:

- **Tissue Injury.** The released contents of injured cells stimulate the release of **mast cell** granules and their potent inflammatory mediators such as histamine, leukotrienes, and prostaglandins. **Histamine** increases the diameter of local blood vessels (vasodilation), causing an increase in blood flow. Histamine also increases the permeability of local capillaries, causing plasma to leak out and form interstitial fluid. This causes the swelling associated with inflammation. Additionally, injured cells, phagocytes, and basophils are sources of

inflammatory mediators, including prostaglandins and leukotrienes.

Leukotrienes attract neutrophils from the blood by chemotaxis and increase vascular permeability. Prostaglandins cause vasodilation by relaxing vascular smooth muscle and are a major cause of the pain associated with inflammation. Nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen relieve pain by inhibiting prostaglandin production.

- *Vasodilation.* Many inflammatory mediators such as histamine are vasodilators that increase the diameters of local capillaries. This causes increased blood flow and is responsible for the heat and redness of inflamed tissue. It allows greater access of the blood to the site of inflammation.
- *Increased Vascular Permeability.* At the same time, inflammatory mediators increase the permeability of the local vasculature, causing leakage of fluid into the interstitial space, resulting in the swelling, or edema, associated with inflammation.
- *Recruitment of Phagocytes.* Leukotrienes are particularly good at attracting neutrophils from the blood to the site of infection by chemotaxis. Following an early neutrophil infiltrate stimulated by macrophage cytokines, more macrophages are recruited to clean up the debris left over at the site. When local infections are severe, neutrophils are attracted to the sites of infections in large numbers, and as they phagocytose the pathogens and subsequently die, their accumulated cellular remains are visible as pus at the infection site.

Overall, inflammation is valuable for many reasons. Not only are the pathogens killed and debris removed, but the increase in vascular permeability encourages the entry of clotting factors, the first step towards wound repair. Inflammation also facilitates the transport of antigen to lymph nodes by dendritic cells for the development of the adaptive immune response.

Chapter Review

Innate immune responses are critical to the early control of infections. Whereas barrier defenses are the body's first line of physical defense against pathogens, innate immune responses are the first line of physiological defense. Innate responses occur rapidly, but with less specificity and effectiveness than the adaptive immune response. Innate responses can be caused by a variety of cells, mediators, and antibacterial proteins such as complement. Within the first few days of an infection, another series of antibacterial proteins are induced, each with activities against certain bacteria, including opsonization of certain species. Additionally, interferons are induced that protect cells from viruses in their vicinity. Finally, the innate immune response does not stop when the adaptive immune response is

developed. In fact, both can cooperate and one can influence the other in their responses against pathogens.

Interactive Link Questions

Exercise:

Problem:

Visit this [website](#) to learn about phagocyte chemotaxis. Phagocyte chemotaxis is the movement of phagocytes according to the secretion of chemical messengers in the form of interleukins and other chemokines. By what means does a phagocyte destroy a bacterium that it has ingested?

Solution:

The bacterium is digested by the phagocyte's digestive enzymes (contained in its lysosomes).

Review Questions

Exercise:

Problem: Which of the following signs is *not* characteristic of inflammation?

- a. redness
 - b. pain
 - c. cold
 - d. swelling
-

Solution:

C

Exercise:

Problem:

Which of the following is *not* important in the antiviral innate immune response?

- a. interferons
- b. natural killer cells
- c. complement
- d. microphages

Solution:

D

Exercise:

Problem:

Enhanced phagocytosis of a cell by the binding of a specific protein is called _____.

- a. endocytosis
- b. opsonization
- c. anaphylaxis
- d. complement activation

Solution:

B

Exercise:

Problem: Which of the following leads to the redness of inflammation?

- a. increased vascular permeability
- b. anaphylactic shock
- c. increased blood flow
- d. complement activation

Solution:

C

Critical Thinking Questions

Exercise:**Problem:**

Describe the process of inflammation in an area that has been traumatized, but not infected.

Solution:

The cell debris and damaged cells induce macrophages to begin to clean them up. Macrophages release cytokines that attract neutrophils, followed by more macrophages. Other mediators released by mast cells increase blood flow to the area and also vascular permeability, allowing the recruited cells to get from the blood to the site of infection, where they can phagocytose the dead cells and debris, preparing the site for wound repair.

Exercise:**Problem:**

Describe two early induced responses and what pathogens they affect.

Solution:

Interferons are produced in virally infected cells and cause them to secrete signals for surrounding cells to make antiviral proteins. C-reactive protein is induced to be made by the liver and will opsonize certain species of bacteria.

Glossary

acute inflammation

inflammation occurring for a limited time period; rapidly developing

chemokine

soluble, long-range, cell-to-cell communication molecule

chronic inflammation

inflammation occurring for long periods of time

complement

enzymatic cascade of constitutive blood proteins that have antipathogen effects, including the direct killing of bacteria

cytokine

soluble, short-range, cell-to-cell communication molecule

early induced immune response

includes antimicrobial proteins stimulated during the first several days of an infection

fas ligand

molecule expressed on cytotoxic T cells and NK cells that binds to the fas molecule on a target cell and induces it to undergo apoptosis

granzyme

apoptosis-inducing substance contained in granules of NK cells and cytotoxic T cells

histamine

vasoactive mediator in granules of mast cells and is the primary cause of allergies and anaphylactic shock

inflammation

basic innate immune response characterized by heat, redness, pain, and swelling

interferons

early induced proteins made in virally infected cells that cause nearby cells to make antiviral proteins

macrophage

ameboid phagocyte found in several tissues throughout the body

mast cell

cell found in the skin and the lining of body cavities that contains cytoplasmic granules with vasoactive mediators such as histamine

monocyte

precursor to macrophages and dendritic cells seen in the blood

neutrophil

phagocytic white blood cell recruited from the bloodstream to the site of infection via the bloodstream

opsonization

enhancement of phagocytosis by the binding of antibody or antimicrobial protein

pattern recognition receptor (PRR)

leukocyte receptor that binds to specific cell wall components of different bacterial species

perforin

molecule in NK cell and cytotoxic T cell granules that form pores in the membrane of a target cell

phagocytosis

movement of material from the outside to the inside of the cells via vesicles made from invaginations of the plasma membrane

The Adaptive Immune Response: T lymphocytes and Their Functional Types

By the end of this section, you will be able to:

- Explain the advantages of the adaptive immune response over the innate immune response
- List the various characteristics of an antigen
- Describe the types of T cell antigen receptors
- Outline the steps of T cell development
- Describe the major T cell types and their functions

Innate immune responses (and early induced responses) are in many cases ineffective at completely controlling pathogen growth. However, they slow pathogen growth and allow time for the adaptive immune response to strengthen and either control or eliminate the pathogen. The innate immune system also sends signals to the cells of the adaptive immune system, guiding them in how to attack the pathogen. Thus, these are the two important arms of the immune response.

The Benefits of the Adaptive Immune Response

The specificity of the adaptive immune response—its ability to specifically recognize and make a response against a wide variety of pathogens—is its great strength. Antigens, the small chemical groups often associated with pathogens, are recognized by receptors on the surface of B and T lymphocytes. The adaptive immune response to these antigens is so versatile that it can respond to nearly any pathogen. This increase in specificity comes because the adaptive immune response has a unique way to develop as many as 10^{11} , or 100 trillion, different receptors to recognize nearly every conceivable pathogen. How could so many different types of antibodies be encoded? And what about the many specificities of T cells? There is not nearly enough DNA in a cell to have a separate gene for each specificity. The mechanism was finally worked out in the 1970s and 1980s using the new tools of molecular genetics

Primary Disease and Immunological Memory

The immune system's first exposure to a pathogen is called a **primary adaptive response**. Symptoms of a first infection, called primary disease, are always relatively severe because it takes time for an initial adaptive immune response to a pathogen to become effective.

Upon re-exposure to the same pathogen, a secondary adaptive immune response is generated, which is stronger and faster than the primary response. The **secondary adaptive response** often eliminates a pathogen before it can cause significant tissue damage or any symptoms. Without symptoms, there is no disease, and the individual is not even aware of the infection. This secondary response is the basis of **immunological memory**, which protects us from getting diseases repeatedly from the same pathogen. By this mechanism, an individual's exposure to pathogens early in life spares the person from these diseases later in life.

Self Recognition

A third important feature of the adaptive immune response is its ability to distinguish between self-antigens, those that are normally present in the body, and foreign antigens, those that might be on a potential pathogen. As T and B cells mature, there are mechanisms in place that prevent them from recognizing self-antigen, preventing a damaging immune response against the body. These mechanisms

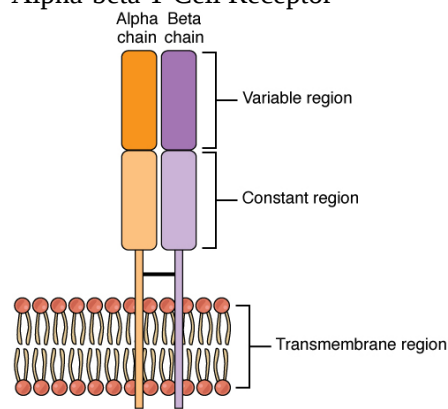
are not 100 percent effective, however, and their breakdown leads to autoimmune diseases, which will be discussed later in this chapter.

T Cell-Mediated Immune Responses

The primary cells that control the adaptive immune response are the lymphocytes, the T and B cells. T cells are particularly important, as they not only control a multitude of immune responses directly, but also control B cell immune responses in many cases as well. Thus, many of the decisions about how to attack a pathogen are made at the T cell level, and knowledge of their functional types is crucial to understanding the functioning and regulation of adaptive immune responses as a whole.

T lymphocytes recognize antigens based on a two-chain protein receptor. The most common and important of these are the alpha-beta T cell receptors ([link](#)).

Alpha-beta T Cell Receptor



Notice the constant and variable regions of each chain, anchored by the transmembrane region.

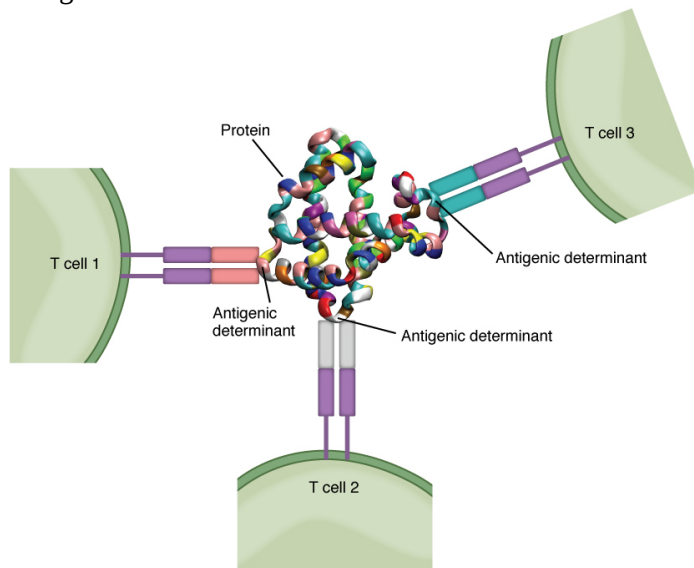
There are two chains in the T cell receptor, and each chain consists of two domains. The **variable region domain** is furthest away from the T cell membrane and is so named because its amino acid sequence varies between receptors. In contrast, the **constant region domain** has less variation. The differences in the amino acid sequences of the variable domains are the molecular basis of the diversity of antigens the receptor can recognize. Thus, the antigen-binding site of the receptor consists of the terminal ends of both receptor chains, and the amino acid sequences of those two areas combine to determine its antigenic specificity. Each T cell produces only one type of receptor and thus is specific for a single particular antigen.

Antigens

Antigens on pathogens are usually large and complex, and consist of many antigenic determinants. An **antigenic determinant** (epitope) is one of the small regions within an antigen to which a receptor can bind, and antigenic determinants are limited by the size of the receptor itself. They usually consist of six or fewer amino acid residues in a protein, or one or two sugar moieties in a carbohydrate antigen. Antigenic determinants on a carbohydrate antigen are usually less diverse than on a protein antigen. Carbohydrate antigens are found on bacterial cell walls and on red blood cells (the ABO blood group antigens). Protein antigens are complex because of the variety of three-dimensional shapes that proteins

can assume, and are especially important for the immune responses to viruses and worm parasites. It is the interaction of the shape of the antigen and the complementary shape of the amino acids of the antigen-binding site that accounts for the chemical basis of specificity ([\[link\]](#)).

Antigenic Determinants

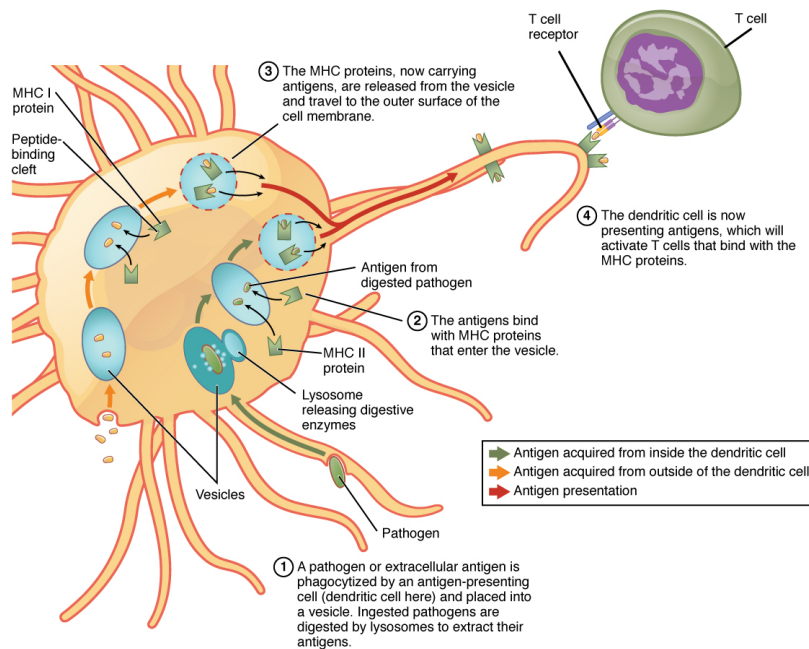


A typical protein antigen has multiple antigenic determinants, shown by the ability of T cells with three different specificities to bind to different parts of the same antigen.

Antigen Processing and Presentation

Although [\[link\]](#) shows T cell receptors interacting with antigenic determinants directly, the mechanism that T cells use to recognize antigens is, in reality, much more complex. T cells do not recognize free-floating or cell-bound antigens as they appear on the surface of the pathogen. They only recognize antigen on the surface of specialized cells called antigen-presenting cells. Antigens are internalized by these cells. **Antigen processing** is a mechanism that enzymatically cleaves the antigen into smaller pieces. The antigen fragments are then brought to the cell's surface and associated with a specialized type of antigen-presenting protein known as a **major histocompatibility complex (MHC)** molecule. The MHC is the cluster of genes that encode these antigen-presenting molecules. The association of the antigen fragments with an MHC molecule on the surface of a cell is known as **antigen presentation** and results in the recognition of antigen by a T cell. This association of antigen and MHC occurs inside the cell, and it is the complex of the two that is brought to the surface. The peptide-binding cleft is a small indentation at the end of the MHC molecule that is furthest away from the cell membrane; it is here that the processed fragment of antigen sits. MHC molecules are capable of presenting a variety of antigens, depending on the amino acid sequence, in their peptide-binding clefts. It is the combination of the MHC molecule and the fragment of the original peptide or carbohydrate that is actually physically recognized by the T cell receptor ([\[link\]](#)).

Antigen Processing and Presentation



Two distinct types of MHC molecules, **MHC class I** and **MHC class II**, play roles in antigen presentation. Although produced from different genes, they both have similar functions. They bring processed antigen to the surface of the cell via a transport vesicle and present the antigen to the T cell and its receptor. Antigens from different classes of pathogens, however, use different MHC classes and take different routes through the cell to get to the surface for presentation. The basic mechanism, though, is the same. Antigens are processed by digestion, are brought into the endomembrane system of the cell, and then are expressed on the surface of the antigen-presenting cell for antigen recognition by a T cell. Intracellular antigens are typical of viruses, which replicate inside the cell, and certain other intracellular parasites and bacteria. These antigens are processed in the cytosol by an enzyme complex known as the proteasome and are then brought into the endoplasmic reticulum by the transporter associated with antigen processing (TAP) system, where they interact with class I MHC molecules and are eventually transported to the cell surface by a transport vesicle.

Extracellular antigens, characteristic of many bacteria, parasites, and fungi that do not replicate inside the cell's cytoplasm, are brought into the endomembrane system of the cell by receptor-mediated endocytosis. The resulting vesicle fuses with vesicles from the Golgi complex, which contain pre-formed MHC class II molecules. After fusion of these two vesicles and the association of antigen and MHC, the new vesicle makes its way to the cell surface.

Professional Antigen-presenting Cells

Many cell types express class I molecules for the presentation of intracellular antigens. These MHC molecules may then stimulate a cytotoxic T cell immune response, eventually destroying the cell and the pathogen within. This is especially important when it comes to the most common class of intracellular pathogens, the virus. Viruses infect nearly every tissue of the body, so all these tissues must necessarily be able to express class I MHC or no T cell response can be made.

On the other hand, class II MHC molecules are expressed only on the cells of the immune system, specifically cells that affect other arms of the immune response. Thus, these cells are called

“professional” antigen-presenting cells to distinguish them from those that bear class I MHC. The three types of professional antigen presenters are macrophages, dendritic cells, and B cells ([link](#)).

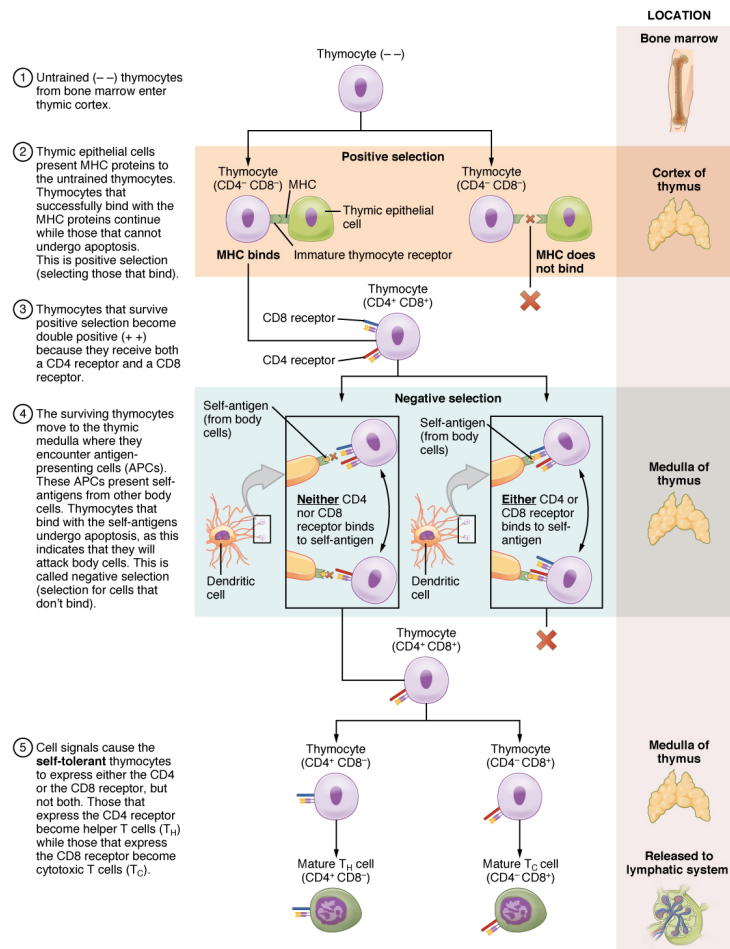
Macrophages stimulate T cells to release cytokines that enhance phagocytosis. Dendritic cells also kill pathogens by phagocytosis (see [link](#)), but their major function is to bring antigens to regional draining lymph nodes. The lymph nodes are the locations in which most T cell responses against pathogens of the interstitial tissues are mounted. Macrophages are found in the skin and in the lining of mucosal surfaces, such as the nasopharynx, stomach, lungs, and intestines. B cells may also present antigens to T cells, which are necessary for certain types of antibody responses, to be covered later in this chapter.

| Classes of Antigen-presenting Cells | | | |
|-------------------------------------|------------|--|--|
| MHC | Cell type | Phagocytic? | Function |
| Class I | Many | No | Stimulates cytotoxic T cell immune response |
| Class II | Macrophage | Yes | Stimulates phagocytosis and presentation at primary infection site |
| Class II | Dendritic | Yes, in tissues | Brings antigens to regional lymph nodes |
| Class II | B cell | Yes, internalizes surface Ig and antigen | Stimulates antibody secretion by B cells |

T Cell Development and Differentiation

The process of eliminating T cells that might attack the cells of one’s own body is referred to as **T cell tolerance**. While thymocytes are in the cortex of the thymus, they are referred to as “double negatives,” meaning that they do not bear the CD4 or CD8 molecules that you can use to follow their pathways of differentiation ([link](#)). In the cortex of the thymus, they are exposed to cortical epithelial cells. In a process known as **positive selection**, double-negative thymocytes bind to the MHC molecules they observe on the thymic epithelia, and the MHC molecules of “self” are selected. This mechanism kills many thymocytes during T cell differentiation. In fact, only two percent of the thymocytes that enter the thymus leave it as mature, functional T cells.

Differentiation of T Cells within the Thymus



Thymocytes enter the thymus and go through a series of developmental stages that ensures both function and tolerance before they leave and become functional components of the adaptive immune response.

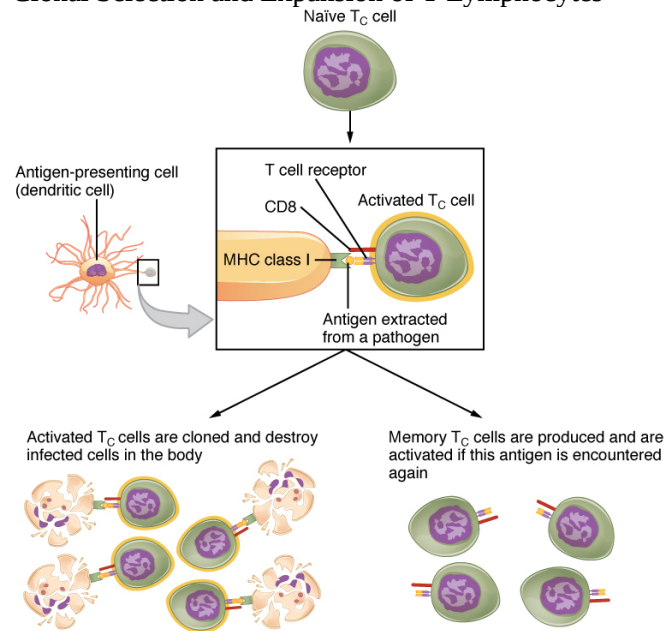
Later, the cells become double positives that express both CD4 and CD8 markers and move from the cortex to the junction between the cortex and medulla. It is here that negative selection takes place. In **negative selection**, self-antigens are brought into the thymus from other parts of the body by professional antigen-presenting cells. The T cells that bind to these self-antigens are selected for negatively and are killed by apoptosis. In summary, the only T cells left are those that can bind to MHC molecules of the body with foreign antigens presented on their binding clefts, preventing an attack on one's own body tissues, at least under normal circumstances. Tolerance can be broken, however, by the development of an autoimmune response, to be discussed later in this chapter.

The cells that leave the thymus become single positives, expressing either CD4 or CD8, but not both (see [link](#)). The CD4⁺ T cells will bind to class II MHC and the CD8⁺ cells will bind to class I MHC. The discussion that follows explains the functions of these molecules and how they can be used to differentiate between the different T cell functional types.

Mechanisms of T Cell-mediated Immune Responses

Mature T cells become activated by recognizing processed foreign antigen in association with a self-MHC molecule and begin dividing rapidly by mitosis. This proliferation of T cells is called **clonal expansion** and is necessary to make the immune response strong enough to effectively control a pathogen. How does the body select only those T cells that are needed against a specific pathogen? Again, the specificity of a T cell is based on the amino acid sequence and the three-dimensional shape of the antigen-binding site formed by the variable regions of the two chains of the T cell receptor ([link](#)). **Clonal selection** is the process of antigen binding only to those T cells that have receptors specific to that antigen. Each T cell that is activated has a specific receptor “hard-wired” into its DNA, and all of its progeny will have identical DNA and T cell receptors, forming clones of the original T cell.

Clonal Selection and Expansion of T Lymphocytes



Stem cells differentiate into T cells with specific receptors, called clones. The clones with receptors specific for antigens on the pathogen are selected for and expanded.

Clonal Selection and Expansion

The clonal selection theory was proposed by Frank Burnet in the 1950s. However, the term clonal selection is not a complete description of the theory, as clonal expansion goes hand in glove with the selection process. The main tenet of the theory is that a typical individual has a multitude (10^{11}) of different types of T cell clones based on their receptors. In this use, a **clone** is a group of lymphocytes that share the same **antigen receptor**. Each clone is necessarily present in the body in low numbers. Otherwise, the body would not have room for lymphocytes with so many specificities.

Only those clones of lymphocytes whose receptors are activated by the antigen are stimulated to proliferate. Keep in mind that most antigens have multiple antigenic determinants, so a T cell response to a typical antigen involves a polyclonal response. A **polyclonal response** is the stimulation of multiple T cell clones. Once activated, the selected clones increase in number and make many copies of each cell

type, each clone with its unique receptor. By the time this process is complete, the body will have large numbers of specific lymphocytes available to fight the infection (see [\[link\]](#)).

The Cellular Basis of Immunological Memory

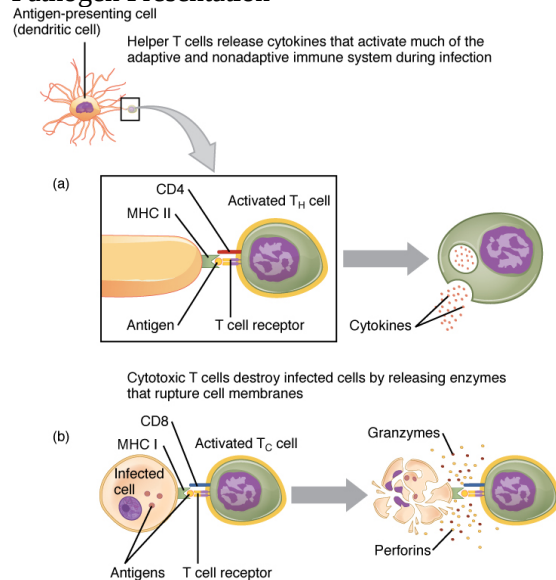
As already discussed, one of the major features of an adaptive immune response is the development of immunological memory.

During a primary adaptive immune response, both **memory T cells** and **effector T cells** are generated. Memory T cells are long-lived and can even persist for a lifetime. Memory cells are primed to act rapidly. Thus, any subsequent exposure to the pathogen will elicit a very rapid T cell response. This rapid, secondary adaptive response generates large numbers of effector T cells so fast that the pathogen is often overwhelmed before it can cause any symptoms of disease. This is what is meant by immunity to a disease. The same pattern of primary and secondary immune responses occurs in B cells and the antibody response, as will be discussed later in the chapter.

T Cell Types and their Functions

In the discussion of T cell development, you saw that mature T cells express either the CD4 marker or the CD8 marker, but not both. These markers are cell adhesion molecules that keep the T cell in close contact with the antigen-presenting cell by directly binding to the MHC molecule (to a different part of the molecule than does the antigen). Thus, T cells and antigen-presenting cells are held together in two ways: by CD4 or CD8 attaching to MHC and by the T cell receptor binding to antigen ([\[link\]](#)).

Pathogen Presentation



(a) CD4 is associated with helper and regulatory T cells. An extracellular pathogen is processed and presented in the binding cleft of a class II MHC molecule, and this interaction is strengthened by the CD4 molecule. (b) CD8 is associated with cytotoxic T cells. An intracellular pathogen is presented by

a class I MHC molecule, and CD8 interacts with it.

Although the correlation is not 100 percent, CD4-bearing T cells are associated with helper functions and CD8-bearing T cells are associated with cytotoxicity. These functional distinctions based on CD4 and CD8 markers are useful in defining the function of each type.

Helper T Cells and their Cytokines

Helper T cells (Th), bearing the CD4 molecule, function by secreting cytokines that act to enhance other immune responses. There are two classes of Th cells, and they act on different components of the immune response. These cells are not distinguished by their surface molecules but by the characteristic set of cytokines they secrete ([\[link\]](#)).

Th1 cells are a type of helper T cell that secretes cytokines that regulate the immunological activity and development of a variety of cells, including macrophages and other types of T cells.

Th2 cells, on the other hand, are cytokine-secreting cells that act on B cells to drive their differentiation into plasma cells that make antibody. In fact, T cell help is required for antibody responses to most protein antigens, and these are called T cell-dependent antigens.

Cytotoxic T cells

Cytotoxic T cells (Tc) are T cells that kill target cells by inducing apoptosis using the same mechanism as NK cells. They either express Fas ligand, which binds to the fas molecule on the target cell, or act by using perforins and granzymes contained in their cytoplasmic granules. As was discussed earlier with NK cells, killing a virally infected cell before the virus can complete its replication cycle results in the production of no infectious particles. As more Tc cells are developed during an immune response, they overwhelm the ability of the virus to cause disease. In addition, each Tc cell can kill more than one target cell, making them especially effective. Tc cells are so important in the antiviral immune response that some speculate that this was the main reason the adaptive immune response evolved in the first place.

Regulatory T Cells

Regulatory T cells (Treg), or suppressor T cells, are the most recently discovered of the types listed here, so less is understood about them. In addition to CD4, they bear the molecules CD25 and FOXP3. Exactly how they function is still under investigation, but it is known that they suppress other T cell immune responses. This is an important feature of the immune response, because if clonal expansion during immune responses were allowed to continue uncontrolled, these responses could lead to autoimmune diseases and other medical issues.

Not only do T cells directly destroy pathogens, but they regulate nearly all other types of the adaptive immune response as well, as evidenced by the functions of the T cell types, their surface markers, the cells they work on, and the types of pathogens they work against (see [\[link\]](#)).

| Functions of T Cell Types and Their Cytokines | | | | | | |
|---|----------------|----------------|---------------|----------------|----------|---------------------------------------|
| T cell | Main target | Function | Pathogen | Surface marker | MHC | Cytokines or mediators |
| Tc | Infected cells | Cytotoxicity | Intracellular | CD8 | Class I | Perforins, granzymes, and fas ligand |
| Th1 | Macrophage | Helper inducer | Extracellular | CD4 | Class II | Interferon- γ and TGF- β |
| Th2 | B cell | Helper inducer | Extracellular | CD4 | Class II | IL-4, IL-6, IL-10, and others |
| Treg | Th cell | Suppressor | None | CD4, CD25 | ? | TGF- β and IL-10 |

Chapter Review

T cells recognize antigens with their antigen receptor, a complex of two protein chains on their surface. They do not recognize self-antigens, however, but only processed antigen presented on their surfaces in a binding groove of a major histocompatibility complex molecule. T cells develop in the thymus, where they learn to use self-MHC molecules to recognize only foreign antigens, thus making them tolerant to self-antigens. There are several functional types of T lymphocytes, the major ones being helper, regulatory, and cytotoxic T cells.

Review Chapter

Exercise:

Problem: T cells that secrete cytokines that help antibody responses are called _____.

- a. Th1
- b. Th2
- c. regulatory T cells
- d. thymocytes

Solution:

B

Exercise:

Problem: The taking in of antigen and digesting it for later presentation is called _____.

- a. antigen presentation
- b. antigen processing
- c. endocytosis
- d. exocytosis

Solution:

B

Exercise:

Problem: Why is clonal expansion so important?

- a. to select for specific cells
- b. to secrete cytokines
- c. to kill target cells
- d. to increase the numbers of specific cells

Solution:

D

Exercise:

Problem: The elimination of self-reactive thymocytes is called _____.

- a. positive selection.
- b. negative selection.
- c. tolerance.
- d. clonal selection.

Solution:

B

Exercise:

Problem: Which type of T cell is most effective against viruses?

- a. Th1
- b. Th2
- c. cytotoxic T cells
- d. regulatory T cells

Solution:

C

Critical Thinking Questions

Exercise:

Problem: Describe the processing and presentation of an intracellular antigen.

Solution:

The antigen is digested by the proteasome, brought into the endoplasmic reticulum by the TAP transporter system, where it binds to class I MHC molecules. These are taken to the cell surface by transport vesicles.

Exercise:

Problem: Describe clonal selection and expansion.

Solution:

Antigen-specific clones are stimulated as their antigen receptor binds to antigen. They are then activated and proliferate, expanding their numbers. The result is a large number of antigen-specific lymphocytes.

Glossary

antigenic determinant

(also, epitope) one of the chemical groups recognized by a single type of lymphocyte antigen receptor

antigen presentation

binding of processed antigen to the protein-binding cleft of a major histocompatibility complex molecule

antigen processing

internalization and digestion of antigen in an antigen-presenting cell

antigen receptor

two-chain receptor by which lymphocytes recognize antigen

clone

group of lymphocytes sharing the same antigen receptor

clonal expansion

growth of a clone of selected lymphocytes

clonal selection

stimulating growth of lymphocytes that have specific receptors

constant region domain

part of a lymphocyte antigen receptor that does not vary much between different receptor types

cytotoxic T cells (Tc)

T lymphocytes with the ability to induce apoptosis in target cells

effector T cells

immune cells with a direct, adverse effect on a pathogen

helper T cells (Th)

T cells that secrete cytokines to enhance other immune responses, involved in activation of both B and T cell lymphocytes

immunological memory

ability of the adaptive immune response to mount a stronger and faster immune response upon re-exposure to a pathogen

major histocompatibility complex (MHC)

gene cluster whose proteins present antigens to T cells

memory T cells

long-lived immune cell reserved for future exposure to an pathogen

MHC class I

found on most cells of the body, it binds to the CD8 molecule on T cells

MHC class II

found on macrophages, dendritic cells, and B cells, it binds to CD4 molecules on T cells

negative selection

selection against thymocytes in the thymus that react with self-antigen

polyclonal response

response by multiple clones to a complex antigen with many determinants

primary adaptive response

immune system's response to the first exposure to a pathogen

positive selection

selection of thymocytes within the thymus that interact with self, but not non-self, MHC molecules

regulatory T cells (Treg)

(also, suppressor T cells) class of CD4 T cells that regulates other T cell responses

secondary adaptive response

immune response observed upon re-exposure to a pathogen, which is stronger and faster than a primary response

T cell tolerance

process during T cell differentiation where most T cells that recognize antigens from one's own body are destroyed

Th1 cells

cells that secrete cytokines that enhance the activity of macrophages and other cells

Th2 cells

cells that secrete cytokines that induce B cells to differentiate into antibody-secreting plasma cells

variable region domain

part of a lymphocyte antigen receptor that varies considerably between different receptor types

The Adaptive Immune Response: B-lymphocytes and Antibodies

By the end of this section, you will be able to:

- Explain how B cells mature and how B cell tolerance develops
- Discuss how B cells are activated and differentiate into plasma cells
- Describe the structure of the antibody classes and their functions

Antibodies were the first component of the adaptive immune response to be characterized by scientists working on the immune system. It was already known that individuals who survived a bacterial infection were immune to re-infection with the same pathogen. Early microbiologists took serum from an immune patient and mixed it with a fresh culture of the same type of bacteria, then observed the bacteria under a microscope. The bacteria became clumped in a process called agglutination. When a different bacterial species was used, the agglutination did not happen. Thus, there was something in the serum of immune individuals that could specifically bind to and agglutinate bacteria.

Scientists now know the cause of the agglutination is an antibody molecule, also called an **immunoglobulin**. What is an antibody? An antibody protein is essentially a secreted form of a B cell receptor. (In fact, surface immunoglobulin is another name for the B cell receptor.) Not surprisingly, the same genes encode both the secreted antibodies and the surface immunoglobulins. One minor difference in the way these proteins are synthesized distinguishes a naïve B cell with antibody on its surface from an antibody-secreting plasma cell with no antibodies on its surface. The antibodies of the plasma cell have the exact same antigen-binding site and specificity as their B cell precursors.

There are five different classes of antibody found in humans: IgM, IgD, IgG, IgA, and IgE. Each of these has specific functions in the immune response, so by learning about them, researchers can learn about the great variety of antibody functions critical to many adaptive immune responses.

B cells do not recognize antigen in the complex fashion of T cells. B cells can recognize native, unprocessed antigen and do not require the participation of MHC molecules and antigen-presenting cells.

B Cell Differentiation and Activation

B cells differentiate in the bone marrow. During the process of maturation, up to 100 trillion different clones of B cells are generated, which is similar to the diversity of antigen receptors seen in T cells.

B cell differentiation and the development of tolerance are not quite as well understood as it is in T cells. **Central tolerance** is the destruction or inactivation of B cells that recognize self-antigens in the bone marrow, and its role is critical and well established. In the process of **clonal deletion**, immature B cells that bind strongly to self-antigens expressed on tissues are signaled to commit suicide by apoptosis, removing them from the population. In the process of **clonal anergy**, however, B cells exposed to soluble antigen in the bone marrow are not physically deleted, but become unable to function.

Another mechanism called peripheral tolerance is a direct result of T cell tolerance. In **peripheral tolerance**, functional, mature B cells leave the bone marrow but have yet to be exposed to self-antigen. Most protein antigens require signals from helper T cells (Th2) to proceed to make antibody. When a B cell binds to a self-antigen but receives no signals from a nearby Th2 cell to produce antibody, the cell is signaled to undergo apoptosis and is destroyed. This is yet another example of the control that T cells have over the adaptive immune response.

After B cells are activated by their binding to antigen, they differentiate into plasma cells. Plasma cells often leave the secondary lymphoid organs, where the response is generated, and migrate back to the bone marrow, where the whole differentiation process started. After secreting antibodies for a specific period, they die, as most of their energy is devoted to making antibodies and not to maintaining themselves. Thus, plasma cells are said to be terminally differentiated.

The final B cell of interest is the memory B cell, which results from the clonal expansion of an activated B cell. Memory B cells function in a way similar to memory T cells. They lead to a stronger and faster secondary response when compared to the primary response, as illustrated below.

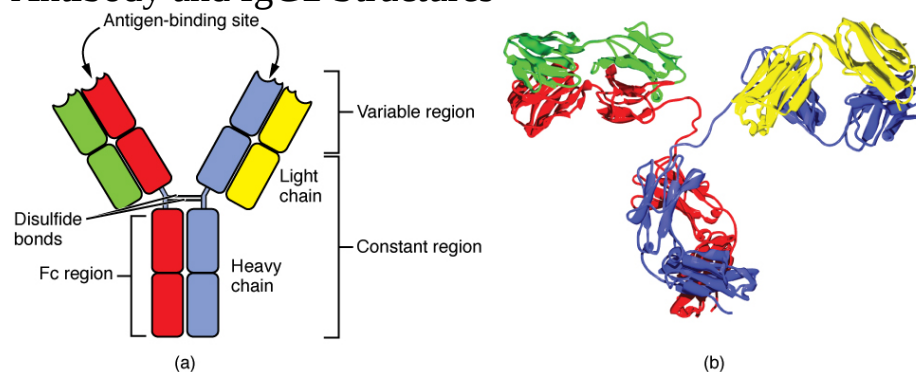
Antibody Structure

Antibodies are glycoproteins consisting of two types of polypeptide chains with attached carbohydrates. The **heavy chain** and the **light chain** are the two polypeptides that form the antibody. The main differences between the classes of antibodies are in the differences between their heavy chains, but as you shall see, the light chains have an important role, forming part of the antigen-binding site on the antibody molecules.

Four-chain Models of Antibody Structures

All antibody molecules have two identical heavy chains and two identical light chains. (Some antibodies contain multiple units of this four-chain structure.) The **Fc region** of the antibody is formed by the two heavy chains coming together, usually linked by disulfide bonds ([link](#)). The Fc portion of the antibody is important in that many effector cells of the immune system have Fc receptors. Cells having these receptors can then bind to antibody-coated pathogens, greatly increasing the specificity of the effector cells. At the other end of the molecule are two identical antigen-binding sites.

Antibody and IgG2 Structures

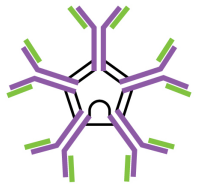

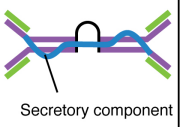

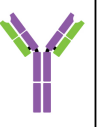


The typical four chain structure of a generic antibody (a) and the corresponding three-dimensional structure of the antibody IgG2 (b).
(credit b: modification of work by Tim Vickers)

Five Classes of Antibodies and their Functions

In general, antibodies have two basic functions. They can act as the B cell antigen receptor or they can be secreted, circulate, and bind to a pathogen, often labeling it for identification by other forms of the immune response. Of the five antibody classes, notice that only two can function as the antigen receptor for naïve B cells: IgM and **IgD** ([\[link\]](#)). Mature B cells that leave the bone marrow express both IgM and IgD, but both antibodies have the same antigen specificity. Only IgM is secreted, however, and no other nonreceptor function for IgD has been discovered.

Five Classes of Antibodies

| The Five Immunoglobulin (Ig) Classes | | | | | |
|---------------------------------------|--|--|--|---|--|
| | IgM pentamer | IgG monomer | Secretory IgA dimer | IgE monomer | IgD monomer |
| |  |  |  |  |  |
| Heavy chains | μ | γ | α | ϵ | δ |
| Number of antigen binding sites | 10 | 2 | 4 | 2 | 2 |
| Molecular weight (Daltons) | 900,000 | 150,000 | 385,000 | 200,000 | 180,000 |
| Percentage of total antibody in serum | 6% | 80% | 13% | 0.002% | 1% |
| Crosses placenta | no | yes | no | no | no |
| Fixes complement | yes | yes | no | no | no |
| Fc binds to | | phagocytes | | mast cells and basophils | |
| Function | Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor | Main blood antibody of secondary responses, neutralizes toxins, opsonization | Secreted into mucus, tears, saliva, colostrum | Antibody of allergy and antiparasitic activity | B cell receptor |

IgM consists of five four-chain structures (20 total chains with 10 identical antigen-binding sites) and is thus the largest of the antibody molecules. IgM is usually the first antibody made during a primary response. Its 10 antigen-

binding sites and large shape allow it to bind well to many bacterial surfaces. It is excellent at binding complement proteins and activating the complement cascade, consistent with its role in promoting chemotaxis, opsonization, and cell lysis. Thus, it is a very effective antibody against bacteria at early stages of a primary antibody response. As the primary response proceeds, the antibody produced in a B cell can change to IgG, IgA, or IgE by the process known as class switching. **Class switching** is the change of one antibody class to another. While the class of antibody changes, the specificity and the antigen-binding sites do not. Thus, the antibodies made are still specific to the pathogen that stimulated the initial IgM response.

IgG is a major antibody of late primary responses and the main antibody of secondary responses in the blood. This is because class switching occurs during primary responses. IgG is a monomeric antibody that clears pathogens from the blood and can activate complement proteins (although not as well as IgM), taking advantage of its antibacterial activities. Furthermore, this class of antibody is the one that crosses the placenta to protect the developing fetus from disease exits the blood to the interstitial fluid to fight extracellular pathogens.

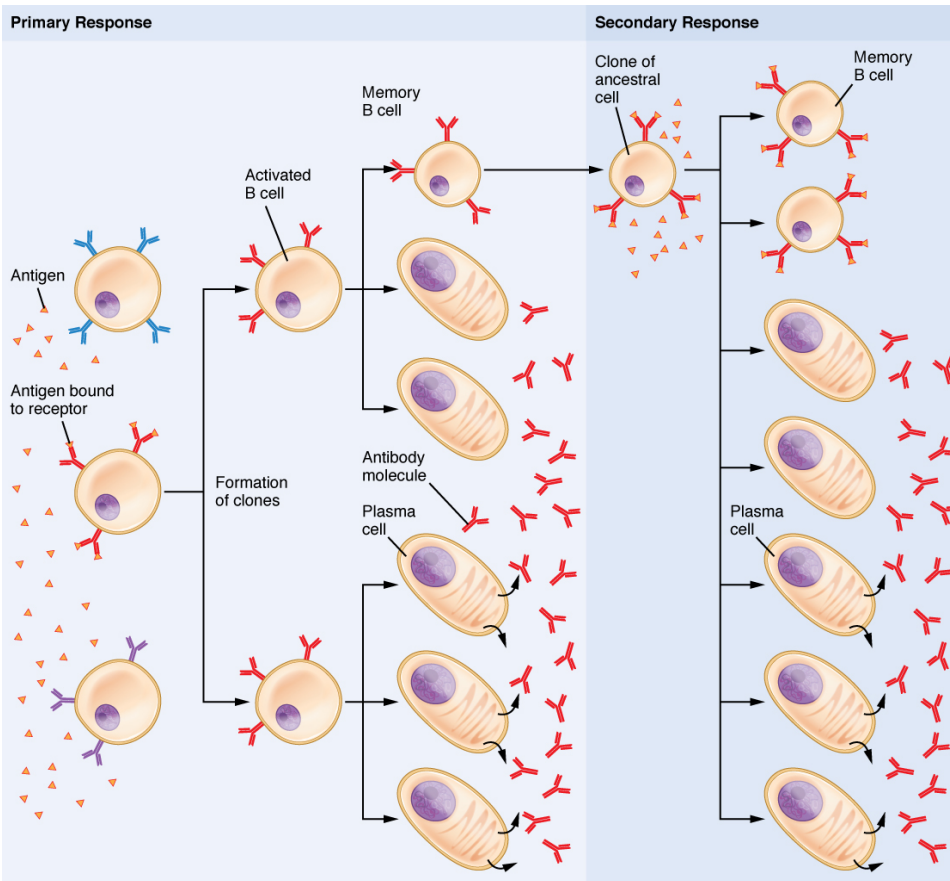
IgA exists in two forms, a four-chain monomer in the blood and an eight-chain structure, or dimer, in exocrine gland secretions of the mucous membranes, including mucus, saliva, and tears. Thus, dimeric IgA is the only antibody to leave the interior of the body to protect body surfaces. IgA is also of importance to newborns, because this antibody is present in mother's breast milk (colostrum), which serves to protect the infant from disease.

IgE is usually associated with allergies and anaphylaxis. It is present in the lowest concentration in the blood, because its Fc region binds strongly to an IgE-specific Fc receptor on the surfaces of mast cells. IgE makes mast cell degranulation very specific, such that if a person is allergic to peanuts, there will be peanut-specific IgE bound to his or her mast cells. In this person, eating peanuts will cause the mast cells to degranulate, sometimes causing severe allergic reactions, including anaphylaxis, a severe, systemic allergic response that can cause death.

Clonal Selection of B Cells

Clonal selection and expansion work much the same way in B cells as in T cells. Only B cells with appropriate antigen specificity are selected for and expanded ([link](#)). Eventually, the plasma cells secrete antibodies with antigenic specificity identical to those that were on the surfaces of the selected B cells. Notice in the figure that both plasma cells and memory B cells are generated simultaneously.

Clonal Selection of B Cells

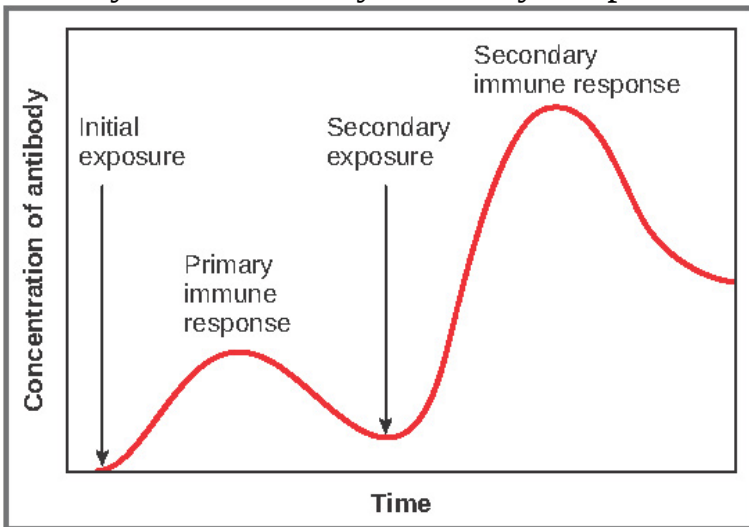


During a primary B cell immune response, both antibody-secreting plasma cells and memory B cells are produced. These memory cells lead to the differentiation of more plasma cells and memory B cells during secondary responses.

Primary versus Secondary B Cell Responses

Primary and secondary responses as they relate to T cells were discussed earlier. This section will look at these responses with B cells and antibody production. Because antibodies are easily obtained from blood samples, they are easy to follow and graph ([link](#)). As you will see from the figure, the primary response to an antigen (representing a pathogen) is delayed by several days. This is the time it takes for the B cell clones to expand and differentiate into plasma cells. The level of antibody produced is low, but it is sufficient for immune protection. The second time a person encounters the same antigen, there is no time delay, and the amount of antibody made is much higher. Thus, the secondary antibody response overwhelms the pathogens quickly and, in most situations, no symptoms are felt. When a different antigen is used, another primary response is made with its low antibody levels and time delay.

Primary and Secondary Antibody Responses



Antigen A is given once to generate a primary response and later to generate a secondary response. When a different antigen is given for the first time, a new primary response is made.

Active versus Passive Immunity

Immunity to pathogens, and the ability to control pathogen growth so that damage to the tissues of the body is limited, can be acquired by (1) the active development of an immune response in the infected individual or (2) the passive transfer of immune components from an immune individual to a nonimmune one. Both active and passive immunity have examples in the natural world and as part of medicine.

Active immunity is the resistance to pathogens acquired during an adaptive immune response within an individual ([link](#)). Naturally acquired active immunity, the response to a pathogen, is the focus of this chapter. Artificially acquired active immunity involves the use of vaccines. A vaccine is a killed or weakened pathogen or its components that, when administered to a healthy individual, leads to the development of immunological memory (a weakened primary immune response) without causing much in the way of symptoms. Thus, with the use of vaccines, one can avoid the damage from disease that results from the first exposure to the pathogen, yet reap the benefits of protection from immunological memory. The advent of vaccines was one of the major medical advances of the twentieth century and led to the eradication of smallpox and the control of many infectious diseases, including polio, measles, and whooping cough.

| Active versus Passive Immunity | | |
|--------------------------------|--|----------------------------|
| | Natural | Artificial |
| Active | Adaptive immune response | Vaccine response |
| Passive | Trans-placental antibodies/breastfeeding | Immune globulin injections |

Passive immunity arises from the transfer of antibodies to an individual without requiring them to mount their own active immune response. Naturally acquired passive immunity is seen during fetal development. IgG is transferred from the maternal circulation to the fetus via the placenta, protecting the fetus from infection and protecting the newborn for the first few months of its life. As already stated, a newborn benefits from the IgA antibodies it obtains from milk during breastfeeding. The fetus and newborn thus benefit from the immunological memory of the mother to the pathogens to which she has been exposed. In medicine, artificially acquired passive immunity usually involves injections of immunoglobulins, taken from animals previously exposed to a specific pathogen. This treatment is a fast-acting method of temporarily protecting an individual who was possibly exposed to a pathogen. The downside to both types of passive immunity is the lack of the development of immunological memory. Once the antibodies are transferred, they are effective for only a limited time before they degrade.

Note:



Immunity can be acquired in an active or passive way, and it can be natural or artificial. Watch this [video](#) to see an animated discussion of passive and active immunity. What is an example of natural immunity acquired passively?

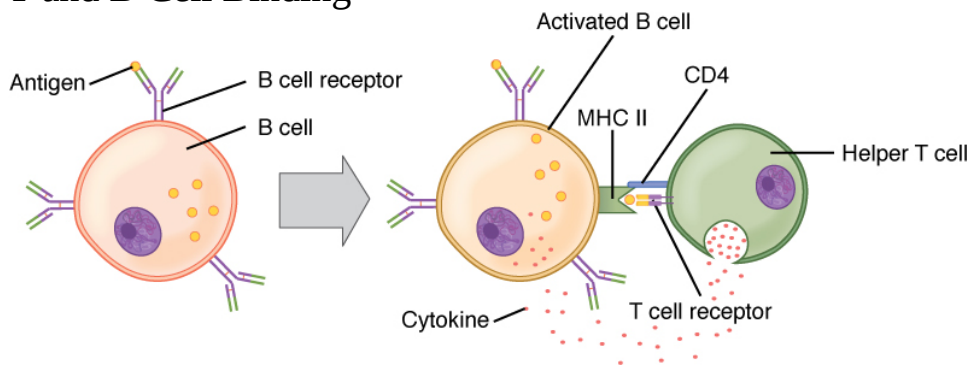
T cell-dependent versus T cell-independent Antigens

As discussed previously, Th2 cells secrete cytokines that drive the production of antibodies in a B cell, responding to complex antigens such as

those made by proteins. On the other hand, some antigens are T cell independent. A **T cell-independent antigen** usually is in the form of repeated carbohydrate moieties found on the cell walls of bacteria. Each antibody on the B cell surface has two binding sites, and the repeated nature of T cell-independent antigen leads to crosslinking of the surface antibodies on the B cell. The crosslinking is enough to activate it in the absence of T cell cytokines.

A **T cell-dependent antigen**, on the other hand, usually is not repeated to the same degree on the pathogen and thus does not crosslink surface antibody with the same efficiency. To elicit a response to such antigens, the B and T cells must come close together ([link](#)). The B cell must receive two signals to become activated. Its surface immunoglobulin must recognize native antigen. Some of this antigen is internalized, processed, and presented to the Th2 cells on a class II MHC molecule. The T cell then binds using its antigen receptor and is activated to secrete cytokines that diffuse to the B cell, finally activating it completely. Thus, the B cell receives signals from both its surface antibody and the T cell via its cytokines, and acts as a professional antigen-presenting cell in the process.

T and B Cell Binding



To elicit a response to a T cell-dependent antigen, the B and T cells must come close together. To become fully activated, the B cell must receive two signals from the native antigen and the T cell's cytokines.

Chapter Review

B cells, which develop within the bone marrow, are responsible for making five different classes of antibodies, each with its own functions. B cells have their own mechanisms for tolerance, but in peripheral tolerance, the B cells that leave the bone marrow remain inactive due to T cell tolerance. Some B cells do not need T cell cytokines to make antibody, and they bypass this need by the crosslinking of their surface immunoglobulin by repeated carbohydrate residues found in the cell walls of many bacterial species. Others require T cells to become activated.

Interactive Link Questions

Exercise:

Problem:

Immunity can be acquired in an active or passive way, and it can be natural or artificial. Watch this [video](#) to see an animated discussion of passive and active immunity. What is an example of natural immunity acquired passively?

Solution:

Breastfeeding is an example of natural immunity acquired passively.

Review Chapter

Exercise:

Problem:

Removing functionality from a B cell without killing it is called _____.

- a. clonal selection
- b. clonal expansion
- c. clonal deletion
- d. clonal anergy

Solution:

D

Exercise:

Problem:

Which class of antibody crosses the placenta in pregnant women?

- a. IgM
- b. IgA
- c. IgE
- d. IgG

Solution:

D

Exercise:

Problem:

Which class of antibody has no known function other than as an antigen receptor?

- a. IgM
- b. IgA
- c. IgE
- d. IgD

Solution:

D

Exercise:

Problem: When does class switching occur?

- a. primary response
 - b. secondary response
 - c. tolerance
 - d. memory response
-

Solution:

A

Exercise:

Problem: Which class of antibody is found in mucus?

- a. IgM
 - b. IgA
 - c. IgE
 - d. IgD
-

Solution:

B

Critical Thinking Questions

Exercise:

Problem: Describe how secondary B cell responses are developed.

Solution:

B cells activated during a primary response differentiate either into terminally differentiated plasma cells or into memory B cells. These memory B cells are what respond during a secondary or memory antibody response.

Exercise:

Problem: Describe the role of IgM in immunity.

Solution:

IgM is an antigen receptor on naïve B cells. Upon activation, naïve B cells make IgM first. IgM is good at binding complement and thus has good antibacterial effects. IgM is replaced with other classes of antibodies later on in the primary response due to class switching.

Glossary

active immunity

immunity developed from an individual's own immune system

central tolerance

B cell tolerance induced in immature B cells of the bone marrow

class switching

ability of B cells to change the class of antibody they produce without altering the specificity for antigen

clonal anergy

process whereby B cells that react to soluble antigens in bone marrow are made nonfunctional

clonal deletion

removal of self-reactive B cells by inducing apoptosis

Fc region

in an antibody molecule, the site where the two termini of the heavy chains come together; many cells have receptors for this portion of the antibody, adding functionality to these molecules

heavy chain

larger protein chain of an antibody

IgA

antibody whose dimer is secreted by exocrine glands, is especially effective against digestive and respiratory pathogens, and can pass immunity to an infant through breastfeeding

IgD

class of antibody whose only known function is as a receptor on naive B cells; important in B cell activation

IgE

antibody that binds to mast cells and causes antigen-specific degranulation during an allergic response

IgG

main blood antibody of late primary and early secondary responses; passed from mother to unborn child via placenta

IgM

antibody whose monomer is a surface receptor of naive B cells; the pentamer is the first antibody made blood plasma during primary responses

immunoglobulin

protein antibody; occurs as one of five main classes

light chain

small protein chain of an antibody

passive immunity

transfer of immunity to a pathogen to an individual that lacks immunity to this pathogen usually by the injection of antibodies

peripheral tolerance

mature B cell made tolerant by lack of T cell help

T cell-dependent antigen

antigen that binds to B cells, which requires signals from T cells to make antibody

T cell-independent antigen

binds to B cells, which do not require signals from T cells to make antibody

The Immune Response against Pathogens

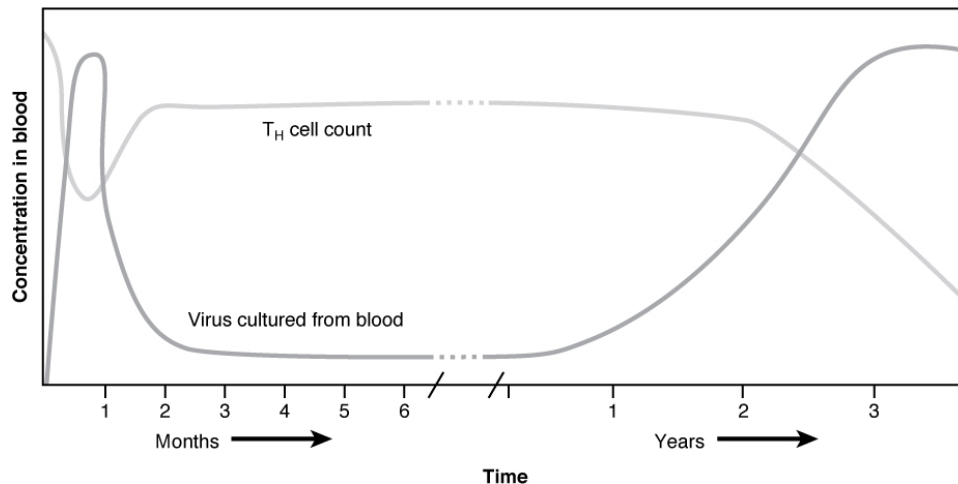
By the end of this section, you will be able to:

- Explain the development of immunological competence
- Describe the mucosal immune response
- Discuss immune responses against bacterial, viral, fungal, and animal pathogens
- Describe different ways pathogens evade immune responses

Now that you understand the development of mature, naïve B cells and T cells, and some of their major functions, how do all of these various cells, proteins, and cytokines come together to actually resolve an infection? Ideally, the immune response will rid the body of a pathogen entirely. The adaptive immune response, with its rapid clonal expansion, is well suited to this purpose. Think of a primary infection as a race between the pathogen and the immune system. The pathogen bypasses barrier defenses and starts multiplying in the host's body. During the first 4 to 5 days, the innate immune response will partially control, but not stop, pathogen growth. As the adaptive immune response gears up, however, it will begin to clear the pathogen from the body, while at the same time becoming stronger and stronger. When following antibody responses in patients with a particular disease such as a virus, this clearance is referred to as seroconversion (sero- = “serum”). **Seroconversion** is the reciprocal relationship between virus levels in the blood and antibody levels. As the antibody levels rise, the virus levels decline, and this is a sign that the immune response is being at least partially effective (partially, because in many diseases, seroconversion does not necessarily mean a patient is getting well).

An excellent example of this is seroconversion during HIV disease ([\[link\]](#)). Notice that antibodies are made early in this disease, and the increase in anti-HIV antibodies correlates with a decrease in detectable virus in the blood. Although these antibodies are an important marker for diagnosing the disease, they are not sufficient to completely clear the virus. Several years later, the vast majority of these individuals, if untreated, will lose their entire adaptive immune response, including the ability to make antibodies, during the final stages of AIDS.

HIV Disease Progression



Seroconversion, the rise of anti-HIV antibody levels and the concomitant decline in measurable virus levels, happens during the first several months of HIV disease. Unfortunately, this antibody response is ineffective at controlling the disease, as seen by the progression of the disease towards AIDS, in which all adaptive immune responses are compromised.

Note:

Everyday Connection

Disinfectants: Fighting the Good Fight?

“Wash your hands!” Parents have been telling their children this for generations. Dirty hands can spread disease. But is it possible to get rid of enough pathogens that children will never get sick? Are children who avoid exposure to pathogens better off? The answers to both these questions appears to be no.

Antibacterial wipes, soaps, gels, and even toys with antibacterial substances embedded in their plastic are ubiquitous in our society. Still, these products do not rid the skin and gastrointestinal tract of bacteria, and it would be harmful to our health if they did. We need these nonpathogenic bacteria on and within our bodies to keep the pathogenic ones from growing. The urge to keep children perfectly clean is thus probably

misguided. Children will get sick anyway, and the later benefits of immunological memory far outweigh the minor discomforts of most childhood diseases. In fact, getting diseases such as chickenpox or measles later in life is much harder on the adult and are associated with symptoms significantly worse than those seen in the childhood illnesses. Of course, vaccinations help children avoid some illnesses, but there are so many pathogens, we will never be immune to them all.

Could over-cleanliness be the reason that allergies are increasing in more developed countries? Some scientists think so. Allergies are based on an IgE antibody response. Many scientists think the system evolved to help the body rid itself of worm parasites. The hygiene theory is the idea that the immune system is geared to respond to antigens, and if pathogens are not present, it will respond instead to inappropriate antigens such as allergens and self-antigens. This is one explanation for the rising incidence of allergies in developed countries, where the response to nonpathogens like pollen, shrimp, and cat dander cause allergic responses while not serving any protective function.

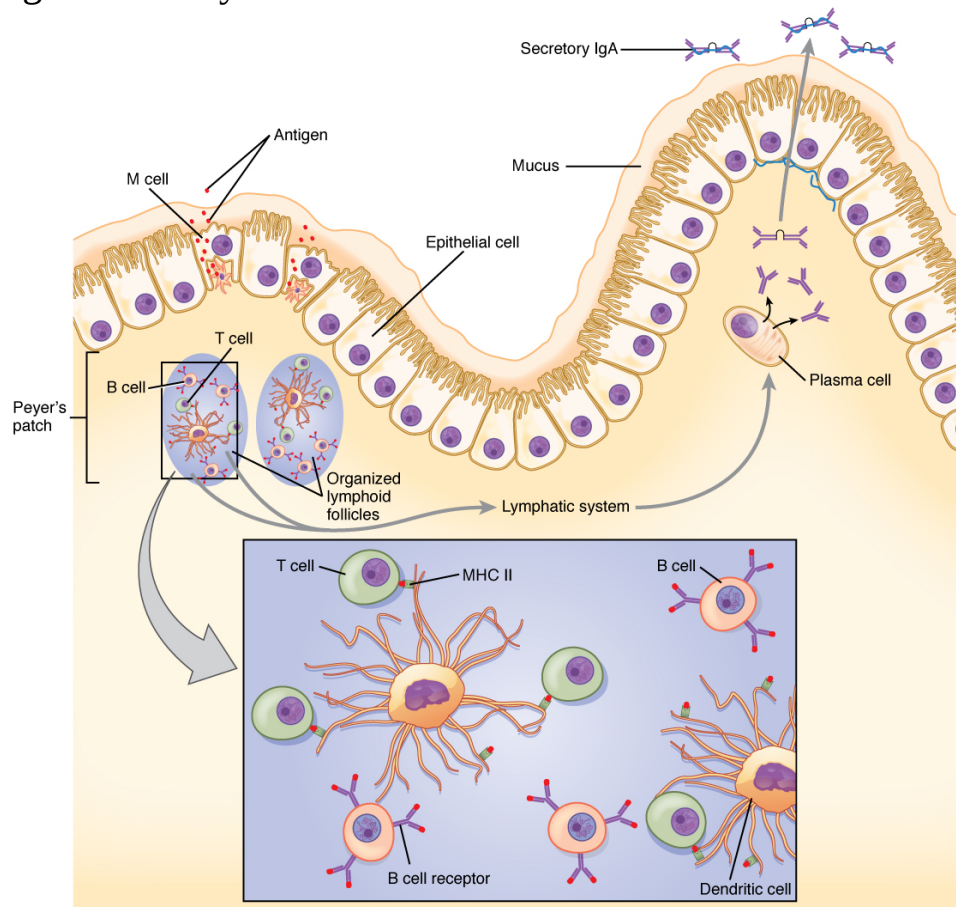
The Mucosal Immune Response

Mucosal tissues are major barriers to the entry of pathogens into the body. The IgA (and sometimes IgM) antibodies in mucus and other secretions can bind to the pathogen, and in the cases of many viruses and bacteria, neutralize them. **Neutralization** is the process of coating a pathogen with antibodies, making it physically impossible for the pathogen to bind to receptors. Neutralization, which occurs in the blood, lymph, and other body fluids and secretions, protects the body constantly. Neutralizing antibodies are the basis for the disease protection offered by vaccines. Vaccinations for diseases that commonly enter the body via mucous membranes, such as influenza, are usually formulated to enhance IgA production.

Immune responses in some mucosal tissues such as the Peyer's patches (see [\[link\]](#)) in the small intestine take up particulate antigens by specialized cells known as microfold or M cells ([\[link\]](#)). These cells allow the body to sample potential pathogens from the intestinal lumen. Dendritic cells then

take the antigen to the regional lymph nodes, where an immune response is mounted.

IgA Immunity



The nasal-associated lymphoid tissue and Peyer's patches of the small intestine generate IgA immunity. Both use M cells to transport antigen inside the body so that immune responses can be mounted.

Defenses against Bacteria and Fungi

The body fights bacterial pathogens with a wide variety of immunological mechanisms, essentially trying to find one that is effective. Bacteria such as *Mycobacterium leprae*, the cause of leprosy, are resistant to lysosomal enzymes and can persist in macrophage organelles or escape into the

cytosol. In such situations, infected macrophages receiving cytokine signals from Th1 cells turn on special metabolic pathways. **Macrophage oxidative metabolism** is hostile to intracellular bacteria, often relying on the production of nitric oxide to kill the bacteria inside the macrophage.

Fungal infections, such as those from *Aspergillus*, *Candida*, and *Pneumocystis*, are largely opportunistic infections that take advantage of suppressed immune responses. Most of the same immune mechanisms effective against bacteria have similar effects on fungi, both of which have characteristic cell wall structures that protect their cells.

Defenses against Parasites

Worm parasites such as helminths are seen as the primary reason why the mucosal immune response, IgE-mediated allergy and asthma, and eosinophils evolved. These parasites were at one time very common in human society. When infecting a human, often via contaminated food, some worms take up residence in the gastrointestinal tract. Eosinophils are attracted to the site by T cell cytokines, which release their granule contents upon their arrival. Mast cell degranulation also occurs, and the fluid leakage caused by the increase in local vascular permeability is thought to have a flushing action on the parasite, expelling its larvae from the body. Furthermore, if IgE labels the parasite, the eosinophils can bind to it by its Fc receptor.

Defenses against Viruses

The primary mechanisms against viruses are NK cells, interferons, and cytotoxic T cells. Antibodies are effective against viruses mostly during protection, where an immune individual can neutralize them based on a previous exposure. Antibodies have no effect on viruses or other intracellular pathogens once they enter the cell, since antibodies are not able to penetrate the plasma membrane of the cell. Many cells respond to viral infections by downregulating their expression of MHC class I molecules. This is to the advantage of the virus, because without class I expression, cytotoxic T cells have no activity. NK cells, however, can recognize virally

infected class I-negative cells and destroy them. Thus, NK and cytotoxic T cells have complementary activities against virally infected cells.

Interferons have activity in slowing viral replication and are used in the treatment of certain viral diseases, such as hepatitis B and C, but their ability to eliminate the virus completely is limited. The cytotoxic T cell response, though, is key, as it eventually overwhelms the virus and kills infected cells before the virus can complete its replicative cycle. Clonal expansion and the ability of cytotoxic T cells to kill more than one target cell make these cells especially effective against viruses. In fact, without cytotoxic T cells, it is likely that humans would all die at some point from a viral infection (if no vaccine were available).

Evasion of the Immune System by Pathogens

It is important to keep in mind that although the immune system has evolved to be able to control many pathogens, pathogens themselves have evolved ways to evade the immune response. An example already mentioned is in *Mycobacterium tuberculosis*, which has evolved a complex cell wall that is resistant to the digestive enzymes of the macrophages that ingest them, and thus persists in the host, causing the chronic disease tuberculosis. This section briefly summarizes other ways in which pathogens can “outwit” immune responses. But keep in mind, although it seems as if pathogens have a will of their own, they do not. All of these evasive “strategies” arose strictly by evolution, driven by selection.

Bacteria sometimes evade immune responses because they exist in multiple strains, such as different groups of *Staphylococcus aureus*. *S. aureus* is commonly found in minor skin infections, such as boils, and some healthy people harbor it in their nose. One small group of strains of this bacterium, however, called methicillin-resistant *Staphylococcus aureus*, has become resistant to multiple antibiotics and is essentially untreatable. Different bacterial strains differ in the antigens on their surfaces. The immune response against one strain (antigen) does not affect the other; thus, the species survives.

Another method of immune evasion is mutation. Because viruses' surface molecules mutate continuously, viruses like influenza change enough each year that the flu vaccine for one year may not protect against the flu common to the next. New vaccine formulations must be derived for each flu season.

Genetic recombination—the combining of gene segments from two different pathogens—is an efficient form of immune evasion. For example, the influenza virus contains gene segments that can recombine when two different viruses infect the same cell. Recombination between human and pig influenza viruses led to the 2010 H1N1 swine flu outbreak.

Pathogens can produce immunosuppressive molecules that impair immune function, and there are several different types. Viruses are especially good at evading the immune response in this way, and many types of viruses have been shown to suppress the host immune response in ways much more subtle than the wholesale destruction caused by HIV.

Chapter Review

Early childhood is a time when the body develops much of its immunological memory that protects it from diseases in adulthood. The components of the immune response that have the maximum effectiveness against a pathogen are often associated with the class of pathogen involved. Bacteria and fungi are especially susceptible to damage by complement proteins, whereas viruses are taken care of by interferons and cytotoxic T cells. Worms are attacked by eosinophils. Pathogens have shown the ability, however, to evade the body's immune responses, some leading to chronic infections or even death. The immune system and pathogens are in a slow, evolutionary race to see who stays on top. Modern medicine, hopefully, will keep the results skewed in humans' favor.

Review Questions

Exercise:

Problem:

Which enzymes in macrophages are important for clearing intracellular bacteria?

- a. metabolic
- b. mitochondrial
- c. nuclear
- d. lysosomal

Solution:

D

Exercise:

Problem:

What type of chronic lung disease is caused by a *Mycobacterium*?

- a. asthma
- b. emphysema
- c. tuberculosis
- d. leprosy

Solution:

C

Exercise:

Problem:

Which type of immune response is most *directly* effective against bacteria?

- a. natural killer cells
- b. complement

- c. cytotoxic T cells
- d. helper T cells

Solution:

B

Exercise:

Problem:

What is the reason that you have to be immunized with a new influenza vaccine each year?

- a. the vaccine is only protective for a year
- b. mutation
- c. macrophage oxidative metabolism
- d. memory response

Solution:

B

Exercise:

Problem:

Which type of immune response works in concert with cytotoxic T cells against virally infected cells?

- a. natural killer cells
- b. complement
- c. antibodies
- d. memory

Solution:

A

Critical Thinking Questions

Exercise:

Problem: Describe how seroconversion works in HIV disease.

Solution:

Seroconversion is the clearance of virus in the serum due to the increase in specific serum antibody levels. Seroconversion happens in the early stages of HIV disease. Unfortunately, the antibody cannot completely clear the virus from the body and thus it most often progresses to AIDS.

Exercise:

Problem: Describe tuberculosis and the innocent bystander effect.

Solution:

Tuberculosis is caused by bacteria resistant to lysosomal enzymes in alveolar macrophages, resulting in chronic infection. The immune response to these bacteria actually causes most of the lung damage that is characteristic of this life-threatening disease.

Glossary

macrophage oxidative metabolism

metabolism turned on in macrophages by T cell signals that help destroy intracellular bacteria

neutralization

inactivation of a virus by the binding of specific antibody

seroconversion

clearance of pathogen in the serum and the simultaneous rise of serum antibody

Diseases Associated with Depressed or Overactive Immune Responses

By the end of this section, you will be able to:

- Discuss inherited and acquired immunodeficiencies
- Explain the four types of hypersensitivity and how they differ
- Give an example of how autoimmune disease breaks tolerance

This section is about how the immune system goes wrong. When it goes haywire, and becomes too weak or too strong, it leads to a state of disease. The factors that maintain immunological homeostasis are complex and incompletely understood.

Immunodeficiencies

As you have seen, the immune system is quite complex. It has many pathways using many cell types and signals. Because it is so complex, there are many ways for it to go wrong. Inherited immunodeficiencies arise from gene mutations that affect specific components of the immune response. There are also acquired immunodeficiencies with potentially devastating effects on the immune system, such as HIV.

Inherited Immunodeficiencies

A list of all inherited immunodeficiencies is well beyond the scope of this book. The list is almost as long as the list of cells, proteins, and signaling molecules of the immune system itself. Some deficiencies, such as those for complement, cause only a higher susceptibility to some Gram-negative bacteria. Others are more severe in their consequences. Certainly, the most serious of the inherited immunodeficiencies is **severe combined immunodeficiency disease (SCID)**. This disease is complex because it is caused by many different genetic defects. What groups them together is the fact that both the B cell and T cell arms of the adaptive immune response are affected.

Children with this disease usually die of opportunistic infections within their first year of life unless they receive a bone marrow transplant. Such a

procedure had not yet been perfected for David Vetter, the “boy in the bubble,” who was treated for SCID by having to live almost his entire life in a sterile plastic cocoon for the 12 years before his death from infection in 1984. One of the features that make bone marrow transplants work as well as they do is the proliferative capability of hematopoietic stem cells of the bone marrow. Only a small amount of bone marrow from a healthy donor is given intravenously to the recipient. It finds its own way to the bone where it populates it, eventually reconstituting the patient’s immune system, which is usually destroyed beforehand by treatment with radiation or chemotherapeutic drugs.

New treatments for SCID using gene therapy, inserting nondefective genes into cells taken from the patient and giving them back, have the advantage of not needing the tissue match required for standard transplants. Although not a standard treatment, this approach holds promise, especially for those in whom standard bone marrow transplantation has failed.

Human Immunodeficiency Virus/AIDS

Although many viruses cause suppression of the immune system, only one wipes it out completely, and that is the previously mentioned HIV. It is worth discussing the biology of this virus, which can lead to the well-known AIDS, so that its full effects on the immune system can be understood. The virus is transmitted through semen, vaginal fluids, and blood, and can be caught by risky sexual behaviors and the sharing of needles by intravenous drug users. There are sometimes, but not always, flu-like symptoms in the first 1 to 2 weeks after infection. This is later followed by seroconversion. The anti-HIV antibodies formed during seroconversion are the basis for most initial HIV screening done in the United States. Because seroconversion takes different lengths of time in different individuals, multiple AIDS tests are given months apart to confirm or eliminate the possibility of infection.

After seroconversion, the amount of virus circulating in the blood drops and stays at a low level for several years. During this time, the levels of CD4⁺ cells, especially helper T cells, decline steadily, until at some point, the

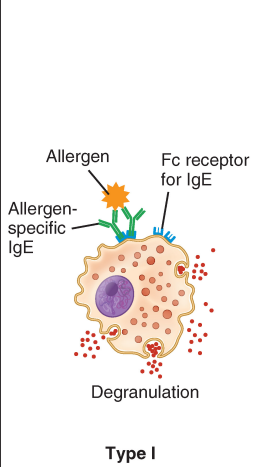
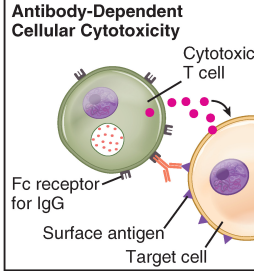
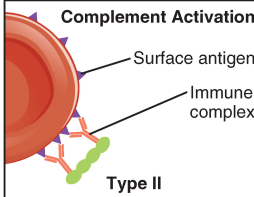
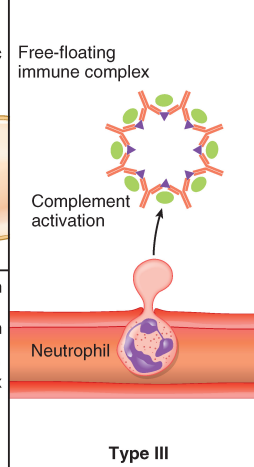
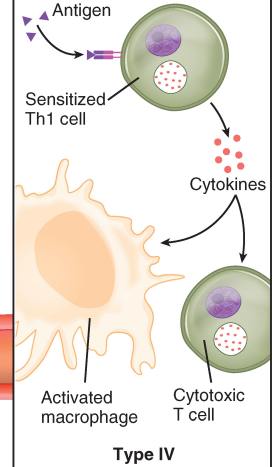
immune response is so weak that opportunistic disease and eventually death result. HIV uses CD4 as the receptor to get inside cells, but it also needs a co-receptor, such as CCR5 or CXCR4. These co-receptors, which usually bind to chemokines, present another target for anti-HIV drug development. Although other antigen-presenting cells are infected with HIV, given that CD4⁺ helper T cells play an important role in T cell immune responses and antibody responses, it should be no surprise that both types of immune responses are eventually seriously compromised.

Treatment for the disease consists of drugs that target virally encoded proteins that are necessary for viral replication but are absent from normal human cells. By targeting the virus itself and sparing the cells, this approach has been successful in significantly prolonging the lives of HIV-positive individuals. On the other hand, an HIV vaccine has been 30 years in development and is still years away. Because the virus mutates rapidly to evade the immune system, scientists have been looking for parts of the virus that do not change and thus would be good targets for a vaccine candidate.

Hypersensitivities

The word “hypersensitivity” simply means sensitive beyond normal levels of activation. Allergies and inflammatory responses to nonpathogenic environmental substances have been observed since the dawn of history. Hypersensitivity is a medical term describing symptoms that are now known to be caused by unrelated mechanisms of immunity. Still, it is useful for this discussion to use the four types of hypersensitivities as a guide to understand these mechanisms ([\[link\]](#)).

Immune Hypersensitivity

| | | | |
|--|--|---|--|
|  <p>Type I</p> | <p>Antibody-Dependent Cellular Cytotoxicity</p>  <p>Complement Activation</p>  <p>Type II</p> |  <p>Type III</p> |  <p>Type IV</p> |
| <p>IgE-Mediated Hypersensitivity</p> | <p>IgG-Mediated Cytotoxic Hypersensitivity</p> | <p>Immune Complex-Mediated Hypersensitivity</p> | <p>Cell-Mediated Hypersensitivity</p> |
| <p>IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.</p> | <p>Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)</p> | <p>Antigen-antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site</p> | <p>Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site</p> |
| <p>Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema</p> | <p>Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis</p> | <p>Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus</p> | <p>Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis</p> |

Components of the immune system cause four types of hypersensitivity. Notice that types I–III are B cell mediated, whereas type IV hypersensitivity is exclusively a T cell phenomenon.

Immediate (Type I) Hypersensitivity

Antigens that cause allergic responses are often referred to as allergens. The specificity of the **immediate hypersensitivity** response is predicated on the binding of allergen-specific IgE to the mast cell surface. The process of producing allergen-specific IgE is called sensitization, and is a necessary prerequisite for the symptoms of immediate hypersensitivity to occur. Allergies and allergic asthma are mediated by mast cell degranulation that is caused by the crosslinking of the antigen-specific IgE molecules on the mast cell surface. The mediators released have various vasoactive effects

already discussed, but the major symptoms of inhaled allergens are the nasal edema and runny nose caused by the increased vascular permeability and increased blood flow of nasal blood vessels. As these mediators are released with mast cell degranulation, **type I hypersensitivity** reactions are usually rapid and occur within just a few minutes, hence the term immediate hypersensitivity.

Most allergens are in themselves nonpathogenic and therefore innocuous. Some individuals develop mild allergies, which are usually treated with antihistamines. Others develop severe allergies that may cause anaphylactic shock, which can potentially be fatal within 20 to 30 minutes if untreated. This drop in blood pressure (shock) with accompanying contractions of bronchial smooth muscle is caused by systemic mast cell degranulation when an allergen is eaten (for example, shellfish and peanuts), injected (by a bee sting or being administered penicillin), or inhaled (asthma). Because epinephrine raises blood pressure and relaxes bronchial smooth muscle, it is routinely used to counteract the effects of anaphylaxis and can be lifesaving. Patients with known severe allergies are encouraged to keep automatic epinephrine injectors with them at all times, especially when away from easy access to hospitals.

Allergists use skin testing to identify allergens in type I hypersensitivity. In skin testing, allergen extracts are injected into the epidermis, and a positive result of a soft, pale swelling at the site surrounded by a red zone (called the wheal and flare response), caused by the release of histamine and the granule mediators, usually occurs within 30 minutes. The soft center is due to fluid leaking from the blood vessels and the redness is caused by the increased blood flow to the area that results from the dilation of local blood vessels at the site.

Type II and Type III Hypersensitivities

Type II hypersensitivity, which involves IgG-mediated lysis of cells by complement proteins, occurs during mismatched blood transfusions and blood compatibility diseases such as erythroblastosis fetalis (see section on transplantation). **Type III hypersensitivity** occurs with diseases such as

systemic lupus erythematosus, where soluble antigens, mostly DNA and other material from the nucleus, and antibodies accumulate in the blood to the point that the antigen and antibody precipitate along blood vessel linings. These immune complexes often lodge in the kidneys, joints, and other organs where they can activate complement proteins and cause inflammation.

Delayed (Type IV) Hypersensitivity

Delayed hypersensitivity, or type IV hypersensitivity, is basically a standard cellular immune response. In delayed hypersensitivity, the first exposure to an antigen is called **sensitization**, such that on re-exposure, a secondary cellular response results, secreting cytokines that recruit macrophages and other phagocytes to the site. These sensitized T cells, of the Th1 class, will also activate cytotoxic T cells. The time it takes for this reaction to occur accounts for the 24- to 72-hour delay in development.

The classical test for delayed hypersensitivity is the tuberculin test for tuberculosis, where bacterial proteins from *M. tuberculosis* are injected into the skin. A couple of days later, a positive test is indicated by a raised red area that is hard to the touch, called an induration, which is a consequence of the cellular infiltrate, an accumulation of activated macrophages. A positive tuberculin test means that the patient has been exposed to the bacteria and exhibits a cellular immune response to it.

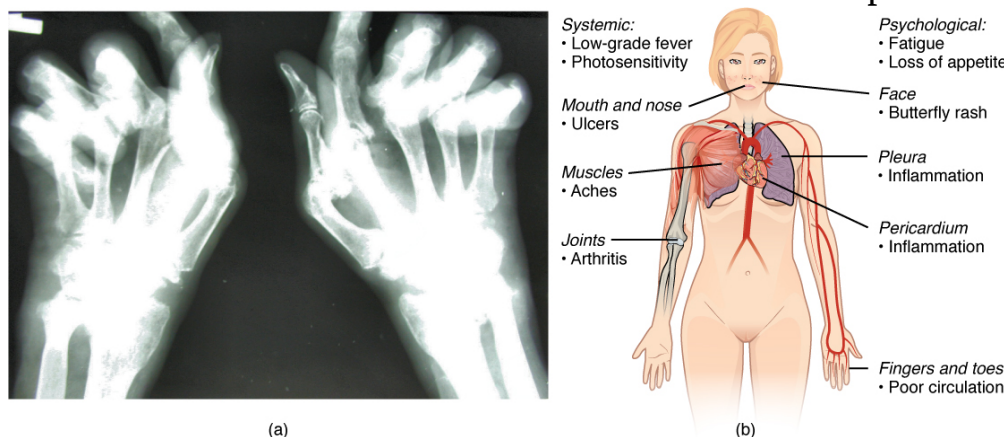
Another type of delayed hypersensitivity is contact sensitivity, where substances such as the metal nickel cause a red and swollen area upon contact with the skin. The individual must have been previously sensitized to the metal. A much more severe case of contact sensitivity is poison ivy, but many of the harshest symptoms of the reaction are associated with the toxicity of its oils and are not T cell mediated.

Autoimmune Responses

The worst cases of the immune system over-reacting are autoimmune diseases. Somehow, tolerance breaks down and the immune systems in

individuals with these diseases begin to attack their own bodies, causing significant damage. The trigger for these diseases is, more often than not, unknown, and the treatments are usually based on resolving the symptoms using immunosuppressive and anti-inflammatory drugs such as steroids. These diseases can be localized and crippling, as in rheumatoid arthritis, or diffuse in the body with multiple symptoms that differ in different individuals, as is the case with systemic lupus erythematosus ([\[link\]](#)).

Autoimmune Disorders: Rheumatoid Arthritis and Lupus



(a) Extensive damage to the right hand of a rheumatoid arthritis sufferer is shown in the x-ray. (b) The diagram shows a variety of possible symptoms of systemic lupus erythematosus.

Environmental triggers seem to play large roles in autoimmune responses. One explanation for the breakdown of tolerance is that, after certain bacterial infections, an immune response to a component of the bacterium cross-reacts with a self-antigen. This mechanism is seen in rheumatic fever, a result of infection with *Streptococcus* bacteria, which causes strep throat. The antibodies to this pathogen's M protein cross-react with an antigenic component of heart myosin, a major contractile protein of the heart that is critical to its normal function. The antibody binds to these molecules and activates complement proteins, causing damage to the heart, especially to the heart valves. On the other hand, some theories propose that having multiple common infectious diseases actually prevents autoimmune responses. The fact that autoimmune diseases are rare in countries that have

a high incidence of infectious diseases supports this idea, another example of the hygiene hypothesis discussed earlier in this chapter.

There are genetic factors in autoimmune diseases as well. Some diseases are associated with the MHC genes that an individual expresses. The reason for this association is likely because if one’s MHC molecules are not able to present a certain self-antigen, then that particular autoimmune disease cannot occur. Overall, there are more than 80 different autoimmune diseases, which are a significant health problem in the elderly. [\[link\]](#) lists several of the most common autoimmune diseases, the antigens that are targeted, and the segment of the adaptive immune response that causes the damage.

| Autoimmune Diseases | | |
|--------------------------|---|---|
| Disease | Autoantigen | Symptoms |
| Celiac disease | Tissue transglutaminase | Damage to small intestine |
| Diabetes mellitus type I | Beta cells of pancreas | Low insulin production; inability to regulate serum glucose |
| Graves’ disease | Thyroid-stimulating hormone receptor (antibody blocks receptor) | Hyperthyroidism |

| Autoimmune Diseases | | |
|----------------------------|--|--------------------------------|
| Disease | Autoantigen | Symptoms |
| Hashimoto's thyroiditis | Thyroid-stimulating hormone receptor (antibody mimics hormone and stimulates receptor) | Hypothyroidism |
| Lupus erythematosus | Nuclear DNA and proteins | Damage of many body systems |
| Myasthenia gravis | Acetylcholine receptor in neuromuscular junctions | Debilitating muscle weakness |
| Rheumatoid arthritis | Joint capsule antigens | Chronic inflammation of joints |

Chapter Review

The immune response can be under-reactive or over-reactive. Suppressed immunity can result from inherited genetic defects or by acquiring viruses. Over-reactive immune responses include the hypersensitivities: B cell- and T cell-mediated immune responses designed to control pathogens, but that lead to symptoms or medical complications. The worst cases of over-reactive immune responses are autoimmune diseases, where an individual's immune system attacks his or her own body because of the breakdown of immunological tolerance. These diseases are more common in the aged, so treating them will be a challenge in the future as the aged population in the world increases.

Review Questions

Exercise:

Problem:

Which type of hypersensitivity involves soluble antigen-antibody complexes?

- a. type I
- b. type II
- c. type III
- d. type IV

Solution:

C

Exercise:

Problem: What causes the delay in delayed hypersensitivity?

- a. inflammation
- b. cytokine release
- c. recruitment of immune cells
- d. histamine release

Solution:

C

Exercise:

Problem:

Which of the following is a critical feature of immediate hypersensitivity?

- a. inflammation
- b. cytotoxic T cells

- c. recruitment of immune cells
 - d. histamine release
-

Solution:

D

Exercise:

Problem:

Which of the following is an autoimmune disease of the heart?

- a. rheumatoid arthritis
 - b. lupus
 - c. rheumatic fever
 - d. Hashimoto's thyroiditis
-

Solution:

C

Exercise:

Problem:

What drug is used to counteract the effects of anaphylactic shock?

- a. epinephrine
 - b. antihistamines
 - c. antibiotics
 - d. aspirin
-

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

Describe anaphylactic shock in someone sensitive to peanuts?

Solution:

The peanuts cause high levels of mast cell degranulation in the throats of these individuals. The histamine released increases vascular permeability, causing edema and (swelling), making breathing difficult. This must be treated with epinephrine as soon as possible.

Exercise:

Problem: Describe rheumatic fever and how tolerance is broken.

Solution:

Antibody response to the cell walls of β -*Streptococcus* cross-reacts with the heart muscle. Complement is then activated and the heart is damaged, leading to abnormal function. Tolerance is broken because heart myosin antigens are similar to antigens on the β - *Streptococcus* bacteria.

Glossary

delayed hypersensitivity

(type IV) T cell-mediated immune response against pathogens infiltrating interstitial tissues, causing cellular infiltrate

immediate hypersensitivity

(type I) IgE-mediated mast cell degranulation caused by crosslinking of surface IgE by antigen

sensitization

first exposure to an antigen

severe combined immunodeficiency disease (SCID)

genetic mutation that affects both T cell and B cell arms of the immune response

type I hypersensitivity

immediate response mediated by mast cell degranulation caused by the crosslinking of the antigen-specific IgE molecules on the mast cell surface

type II hypersensitivity

cell damage caused by the binding of antibody and the activation of complement, usually against red blood cells

type III hypersensitivity

damage to tissues caused by the deposition of antibody-antigen (immune) complexes followed by the activation of complement

Transplantation and Cancer Immunology

By the end of this section, you will be able to:

- Explain why blood typing is important and what happens when mismatched blood is used in a transfusion
- Describe how tissue typing is done during organ transplantation and the role of transplant anti-rejection drugs
- Show how the immune response is able to control some cancers and how this immune response might be enhanced by cancer vaccines

The immune responses to transplanted organs and to cancer cells are both important medical issues. With the use of tissue typing and anti-rejection drugs, transplantation of organs and the control of the anti-transplant immune response have made huge strides in the past 50 years. Today, these procedures are commonplace. **Tissue typing** is the determination of MHC molecules in the tissue to be transplanted to better match the donor to the recipient. The immune response to cancer, on the other hand, has been more difficult to understand and control. Although it is clear that the immune system can recognize some cancers and control them, others seem to be resistant to immune mechanisms.

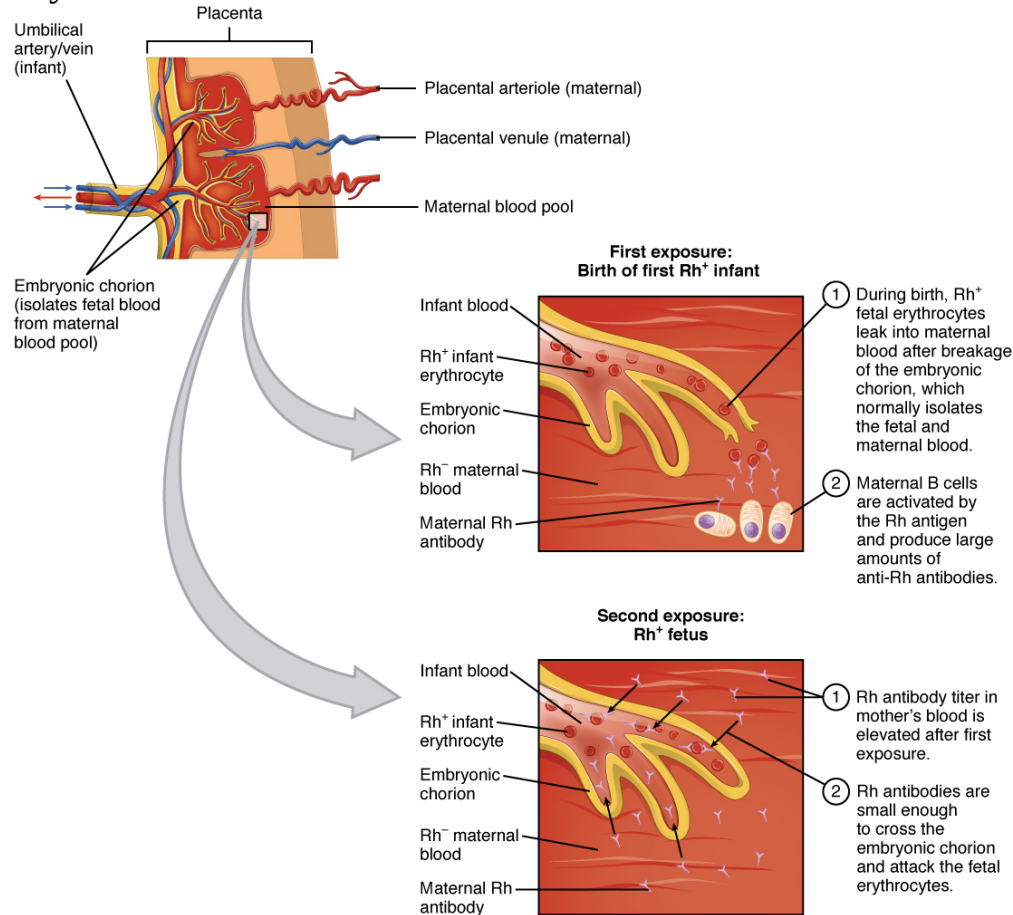
The Rh Factor

Red blood cells can be typed based on their surface antigens. ABO blood type, in which individuals are type A, B, AB, or O according to their genetics, is one example. A separate antigen system seen on red blood cells is the Rh antigen. When someone is “A positive” for example, the positive refers to the presence of the Rh antigen, whereas someone who is “A negative” would lack this molecule.

An interesting consequence of Rh factor expression is seen in **erythroblastosis fetalis**, a hemolytic disease of the newborn ([\[link\]](#)). This disease occurs when mothers negative for Rh antigen have multiple Rh-positive children. During the birth of a first Rh-positive child, the mother makes a primary anti-Rh antibody response to the fetal blood cells that enter the maternal bloodstream. If the mother has a second Rh-positive child, IgG antibodies against Rh-positive blood mounted during this

secondary response cross the placenta and attack the fetal blood, causing anemia. This is a consequence of the fact that the fetus is not genetically identical to the mother, and thus the mother is capable of mounting an immune response against it. This disease is treated with antibodies specific for Rh factor. These are given to the mother during the first and subsequent births, destroying any fetal blood that might enter her system and preventing the immune response.

Erythroblastosis Fetalis



Erythroblastosis fetalis (hemolytic disease of the newborn) is the result of an immune response in an Rh-negative mother who has multiple children with an Rh-positive father. During the first birth, fetal blood enters the mother's circulatory system, and anti-Rh antibodies are made. During the gestation of the second child, these antibodies cross the placenta and attack the blood of the fetus. The treatment for this disease is to give the mother

anti-Rh antibodies (RhoGAM) during the first pregnancy to destroy Rh-positive fetal red blood cells from entering her system and causing the anti-Rh antibody response in the first place.

Tissue Transplantation

Tissue transplantation is more complicated than blood transfusions because of two characteristics of MHC molecules. These molecules are the major cause of transplant rejection (hence the name “histocompatibility”). **MHC polygeny** refers to the multiple MHC proteins on cells, and **MHC polymorphism** refers to the multiple alleles for each individual MHC locus. Thus, there are many alleles in the human population that can be expressed ([\[link\]](#) and [\[link\]](#)). When a donor organ expresses MHC molecules that are different from the recipient, the latter will often mount a cytotoxic T cell response to the organ and reject it. Histologically, if a biopsy of a transplanted organ exhibits massive infiltration of T lymphocytes within the first weeks after transplant, it is a sign that the transplant is likely to fail. The response is a classical, and very specific, primary T cell immune response. As far as medicine is concerned, the immune response in this scenario does the patient no good at all and causes significant harm.

| Partial Table of Alleles of the Human MHC (Class I) | | |
|---|--------------|--|
| Gene | # of alleles | # of possible MHC I protein components |
| A | 2132 | 1527 |

| Partial Table of Alleles of the Human MHC (Class I) | | |
|--|---------------------|---|
| Gene | # of alleles | # of possible MHC I protein components |
| B | 2798 | 2110 |
| C | 1672 | 1200 |
| E | 11 | 3 |
| F | 22 | 4 |
| G | 50 | 16 |

| Partial Table of Alleles of the Human MHC (Class II) | | |
|---|---------------------|--|
| Gene | # of alleles | # of possible MHC II protein components |
| DRA | 7 | 2 |
| DRB | 1297 | 958 |
| DQA1 | 49 | 31 |
| DQB1 | 179 | 128 |
| DPA1 | 36 | 18 |
| DPB1 | 158 | 136 |

| Partial Table of Alleles of the Human MHC (Class II) | | |
|---|---------------------|--|
| Gene | # of alleles | # of possible MHC II protein components |
| DMA | 7 | 4 |
| DMB | 13 | 7 |
| DOA | 12 | 3 |
| DOB | 13 | 5 |

Immunosuppressive drugs such as cyclosporine A have made transplants more successful, but matching the MHC molecules is still key. In humans, there are six MHC molecules that show the most polymorphisms, three class I molecules (A, B, and C) and three class II molecules called DP, DQ, and DR. A successful transplant usually requires a match between at least 3–4 of these molecules, with more matches associated with greater success. Family members, since they share a similar genetic background, are much more likely to share MHC molecules than unrelated individuals do. In fact, due to the extensive polymorphisms in these MHC molecules, unrelated donors are found only through a worldwide database. The system is not foolproof however, as there are not enough individuals in the system to provide the organs necessary to treat all patients needing them.

One disease of transplantation occurs with bone marrow transplants, which are used to treat various diseases, including SCID and leukemia. Because the bone marrow cells being transplanted contain lymphocytes capable of mounting an immune response, and because the recipient's immune response has been destroyed before receiving the transplant, the donor cells may attack the recipient tissues, causing **graft-versus-host disease**. Symptoms of this disease, which usually include a rash and damage to the liver and mucosa, are variable, and attempts have been made to moderate the disease by first removing mature T cells from the donor bone marrow before transplanting it.

Immune Responses Against Cancer

It is clear that with some cancers, for example Kaposi's sarcoma, a healthy immune system does a good job at controlling them ([\[link\]](#)). This disease, which is caused by the human herpesvirus, is almost never observed in individuals with strong immune systems, such as the young and immunocompetent. Other examples of cancers caused by viruses include liver cancer caused by the hepatitis B virus and cervical cancer caused by the human papilloma virus. As these last two viruses have vaccines available for them, getting vaccinated can help prevent these two types of cancer by stimulating the immune response.

Kaposi's Sarcoma Lesions



(credit: National Cancer Institute)

On the other hand, as cancer cells are often able to divide and mutate rapidly, they may escape the immune response, just as certain pathogens such as HIV do. There are three stages in the immune response to many cancers: elimination, equilibrium, and escape. Elimination occurs when the immune response first develops toward tumor-specific antigens specific to the cancer and actively kills most cancer cells, followed by a period of controlled equilibrium during which the remaining cancer cells are held in check. Unfortunately, many cancers mutate, so they no longer express any specific antigens for the immune system to respond to, and a subpopulation

of cancer cells escapes the immune response, continuing the disease process.

This fact has led to extensive research in trying to develop ways to enhance the early immune response to completely eliminate the early cancer and thus prevent a later escape. One method that has shown some success is the use of cancer vaccines, which differ from viral and bacterial vaccines in that they are directed against the cells of one's own body. Treated cancer cells are injected into cancer patients to enhance their anti-cancer immune response and thereby prolong survival. The immune system has the capability to detect these cancer cells and proliferate faster than the cancer cells do, overwhelming the cancer in a similar way as they do for viruses. Cancer vaccines have been developed for malignant melanoma, a highly fatal skin cancer, and renal (kidney) cell carcinoma. These vaccines are still in the development stages, but some positive and encouraging results have been obtained clinically.

It is tempting to focus on the complexity of the immune system and the problems it causes as a negative. The upside to immunity, however, is so much greater: The benefit of staying alive far outweighs the negatives caused when the system does sometimes go awry. Working on "autopilot," the immune system helps to maintain your health and kill pathogens. The only time you really miss the immune response is when it is not being effective and illness results, or, as in the extreme case of HIV disease, the immune system is gone completely.

Note:

Everyday Connection

How Stress Affects the Immune Response: The Connections between the Immune, Nervous, and Endocrine Systems of the Body

The immune system cannot exist in isolation. After all, it has to protect the entire body from infection. Therefore, the immune system is required to interact with other organ systems, sometimes in complex ways. Thirty years of research focusing on the connections between the immune system, the central nervous system, and the endocrine system have led to a new science with the unwieldy name of called **psychoneuroimmunology**. The

physical connections between these systems have been known for centuries: All primary and secondary organs are connected to sympathetic nerves. What is more complex, though, is the interaction of neurotransmitters, hormones, cytokines, and other soluble signaling molecules, and the mechanism of “crosstalk” between the systems. For example, white blood cells, including lymphocytes and phagocytes, have receptors for various neurotransmitters released by associated neurons. Additionally, hormones such as cortisol (naturally produced by the adrenal cortex) and prednisone (synthetic) are well known for their abilities to suppress T cell immune mechanisms, hence, their prominent use in medicine as long-term, anti-inflammatory drugs.

One well-established interaction of the immune, nervous, and endocrine systems is the effect of stress on immune health. In the human vertebrate evolutionary past, stress was associated with the fight-or-flight response, largely mediated by the central nervous system and the adrenal medulla. This stress was necessary for survival. The physical action of fighting or running, whichever the animal decides, usually resolves the problem in one way or another. On the other hand, there are no physical actions to resolve most modern day stresses, including short-term stressors like taking examinations and long-term stressors such as being unemployed or losing a spouse. The effect of stress can be felt by nearly every organ system, and the immune system is no exception ([\[link\]](#)).

Effects of Stress on Body Systems

| System | Stress-related illness |
|----------------------|-------------------------------|
| Integumentary system | Acne, skin rashes, irritation |

Effects of Stress on Body Systems

| System | Stress-related illness |
|-------------------------------|--|
| Nervous system | Headaches, depression, anxiety, irritability, loss of appetite, lack of motivation, reduced mental performance |
| Muscular and skeletal systems | Muscle and joint pain, neck and shoulder pain |
| Circulatory system | Increased heart rate, hypertension, increased probability of heart attacks |
| Digestive system | Indigestion, heartburn, stomach pain, nausea, diarrhea, constipation, weight gain or loss |
| Immune system | Depressed ability to fight infections |
| Male reproductive system | Lowered sperm production, impotence, reduced sexual desire |
| Female reproductive system | Irregular menstrual cycle, reduced sexual desire |

At one time, it was assumed that all types of stress reduced all aspects of the immune response, but the last few decades of research have painted a different picture. First, most short-term stress does not impair the immune system in healthy individuals enough to lead to a greater incidence of diseases. However, older individuals and those with suppressed immune responses due to disease or immunosuppressive drugs may respond even to short-term stressors by getting sicker more often. It has been found that

short-term stress diverts the body's resources towards enhancing innate immune responses, which have the ability to act fast and would seem to help the body prepare better for possible infections associated with the trauma that may result from a fight-or-flight exchange. The diverting of resources away from the adaptive immune response, however, causes its own share of problems in fighting disease.

Chronic stress, unlike short-term stress, may inhibit immune responses even in otherwise healthy adults. The suppression of both innate and adaptive immune responses is clearly associated with increases in some diseases, as seen when individuals lose a spouse or have other long-term stresses, such as taking care of a spouse with a fatal disease or dementia. The new science of psychoneuroimmunology, while still in its relative infancy, has great potential to make exciting advances in our understanding of how the nervous, endocrine, and immune systems have evolved together and communicate with each other.

Chapter Review

Blood transfusion and organ transplantation both require an understanding of the immune response to prevent medical complications. Blood needs to be typed so that natural antibodies against mismatched blood will not destroy it, causing more harm than good to the recipient. Transplanted organs must be matched by their MHC molecules and, with the use of immunosuppressive drugs, can be successful even if an exact tissue match cannot be made. Another aspect to the immune response is its ability to control and eradicate cancer. Although this has been shown to occur with some rare cancers and those caused by known viruses, the normal immune response to most cancers is not sufficient to control cancer growth. Thus, cancer vaccines designed to enhance these immune responses show promise for certain types of cancer.

Review Questions

Exercise:

Problem: Which of the following terms means “many genes”?

- a. polymorphism
- b. polygeny
- c. polypeptide
- d. multiple alleles

Solution:

B

Exercise:

Problem: Why do we have natural antibodies?

- a. We don't know why.
- b. immunity to environmental bacteria
- c. immunity to transplants
- d. from clonal selection

Solution:

B

Exercise:

Problem: Which type of cancer is associated with HIV disease?

- a. Kaposi's sarcoma
- b. melanoma
- c. lymphoma
- d. renal cell carcinoma

Solution:

A

Exercise:

Problem:How does cyclosporine A work?

- a. suppresses antibodies
 - b. suppresses T cells
 - c. suppresses macrophages
 - d. suppresses neutrophils
-

Solution:

B

Exercise:

Problem:What disease is associated with bone marrow transplants?

- a. diabetes mellitus type I
 - b. melanoma
 - c. headache
 - d. graft-versus-host disease
-

Solution:

D

Critical Thinking Questions

Exercise:

Problem:Describe how stress affects immune responses.

Solution:

Stress causes the release of hormones and the activation of nerves that suppress the immune response. Short-term stress has little effect on the health of an already healthy individual, whereas chronic stress does lead to increases in disease in such people.

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Glossary

erythroblastosis fetalis

disease of Rh factor-positive newborns in Rh-negative mothers with multiple Rh-positive children; resulting from the action of maternal antibodies against fetal blood

graft-versus-host disease

in bone marrow transplants; occurs when the transplanted cells mount an immune response against the recipient

MHC polygeny

multiple MHC genes and their proteins found in body cells

MHC polymorphism

multiple alleles for each individual MHC locus

psychoneuroimmunology

study of the connections between the immune, nervous, and endocrine systems

tissue typing

typing of MHC molecules between a recipient and donor for use in a potential transplantation procedure